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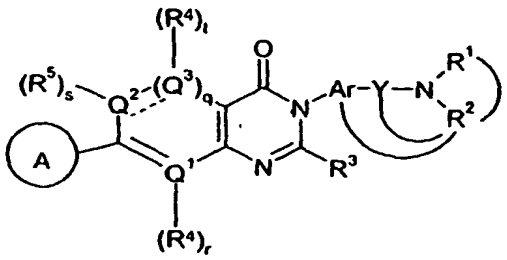
(54) Title: HETEROCYCLIC MCHR1 ANTAGONISTS



(I)

(57) Abstract: This invention relates to novel heterocycles which are antagonists at the melanin-concentrating hormone receptor 1 (MCHR1), also referred to as 11CBy, to pharmaceutical compositions containing them, to processes for their preparation, and to their use in medicines. Compounds of the invention have formula (I).

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HETEROCYCLIC MCHR1 ANTAGONISTS

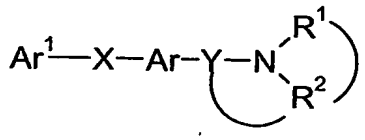
This invention relates to novel heterocycles which are antagonists at the melanin-concentrating hormone receptor 1 (MCHR1), also referred to as 11CBy, to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy.

BACKGROUND OF THE INVENTION

Obesity is a medical condition that is reaching epidemic proportions among humans in a number of countries throughout the world. It is a condition that is also associated with or induces other diseases or conditions that disrupt life activities and lifestyles. Obesity is recognized as a serious risk factor for other diseases and conditions such as diabetes, hypertension, and arteriosclerosis. It is also known that increased body weight due to obesity can place a burden on joints, such as knee joints, causing arthritis, pain, and stiffness.

Because overeating and obesity have become such a problem in the general population, many individuals are now interested in losing weight, reducing weight, and/or maintaining a healthy body weight and desirable lifestyle.

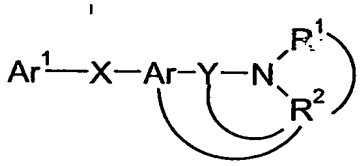
WO01/21577 (Takeda) relates to a compound of the formula



wherein Ar^1 is a cyclic group which may have substituents, X is a spacer having a main chain of 1 to 6 atoms, Y is a bond or a spacer having a main chain of 1 to 6 atoms, Ar is a monocyclic aromatic ring which may be condensed with a 4 to 8 membered non-aromatic ring, and may have further substituents; R^1 and R^2 are independently hydrogen or a hydrocarbon group which may have substituents; R^1 and R^2 together with the adjacent nitrogen atom may form a nitrogen containing hetero ring which may have substituents; R^2 may form a spiro ring together with Ar; or R^2 together with the

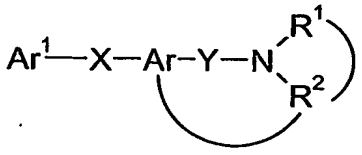
adjacent nitrogen atom may form a nitrogen containing hetero ring which may have substituents; or a salt thereof; and which compounds are antagonists of a melanin-concentrating hormone. Such compounds are suggested as being useful for preventing or treating obesity.

WO 01/82925A1 (Takeda) relates to a compound of the formula



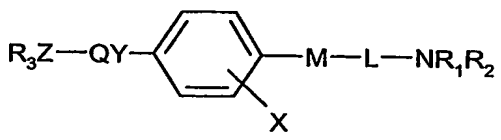
wherein Ar^1 is an optionally substituted cyclic group;
X and Y are the same or different spacers having from 1 to 6 atoms in the main chain;
Ar is an optionally substituted fused polycyclic aromatic ring;
R^1 and R^2 are the same or different hydrogen atoms or optionally substituted hydrocarbon groups, or R^1 and R^2 together with the adjacent nitrogen atoms may form an optionally substituted nitrogenous heterocycle, R^2 together with the adjacent nitrogen atom and Y may form an optionally substituted nitrogenous heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogenous heterocycle or salts thereof.

WO 01/21577A2 (Takeda) relates to aromatic compounds of the formula



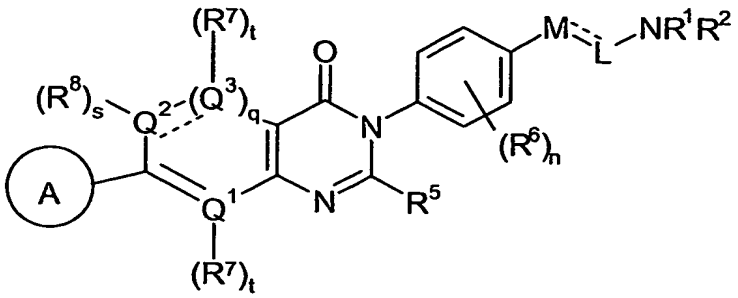
or a salt thereof, which is useful as an agent for preventing or treating obesity.

P32897WO1 (GlaxoSmithKline) relates to compounds of the formula



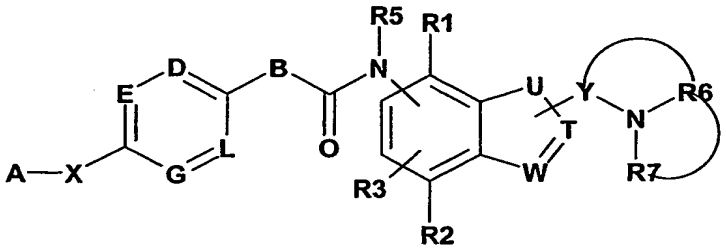
or a salt thereof , wherein M is a group selected from O, S, CO, NH or CH_2, L is a 2 or 3 membered alkylene chain, and the chain -M-L may be optionally substituted by one or more groups selected from methyl, ethyl, hydroxy or alkoxy and or which chain may contain a -C=C- double bond; R_1 and R_2 each independently represent hydrogen, C_{1-6} straight or branched alkyl which may be optionally substituted by phenyl, or C_{3-6} cycloalkyl optionally substituted by one or more C_{1-6} alkyl groups; or R_1 and R_2 together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclic ring or a 7-10 membered bridged heterocyclic ring, which rings may be optionally substituted by a phenyl group or up to 4 C_{1-3} alkyl groups; or R_1 or R_2 may be linked to the group L or be linked as part of the substituted X on the phenyl ring to form a cyclic group; the group X may be linked to the group L to form a cyclic group which may contain an additional oxygen, a sulphur or nitrogen atom, alternatively or additionally there may be one or more substituents X selected from hydroxy, C_{1-2} alkyl, C_{1-2} alkoxy, halogen, C_{2-3} alkenyl, benzyl, CR_aNOR_b wherein R_a and R_b are independently hydrogen or methyl, methoxymethyl, methoxymethoxy or methoxyethoxy; QY is a bicyclic fused heterocyclic ring wherein Y is one ring of a bicyclic fused heterocyclic group and which is linked via nitrogen atom therein to the phenyl ring, and substituted on the second ring Q by the group ZR_3; Z is a bond or a group selected from NH, NCH_3 O, S or CH_2; R_3 is a group selected from aryl, 2-alkenyl, cycloalkyl or 2-cycloalkenyl and which R_3 group may be optionally substituted by one or more C_{1-3} alkyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-3} alkoxy, cyano, trifluoromethyl or methylthio groups, processes for their preparation, pharmaceutical compositions containing them and to their use in medicine.

P32897WO2 (GlaxoSmithKline) relates to a compound of the formula comprising:



a pharmaceutically acceptable salt or solvate thereof, formulations, processes of preparing, and methods of administering to mammals are provided.

Aventis WO 03/015769A1 relates to aminoalkyl-substituted aromatic compounds of the formula below, their physiologically funcitonal derivatives and salts, as well as a method for a the production thereof. Said compounds can be suitably used as anorectic drugs.

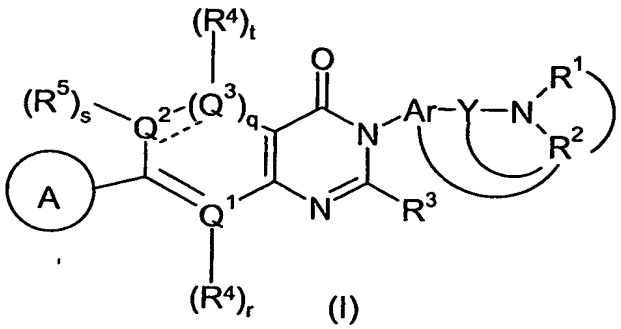


In particular, it is known that melanin-concentrating hormone ("MCH") originates in the hypothalamus and has orexigenic action (see Nature, Vol. 396, p. 670, (1998), for example). There is an on-going need for the development of a melanin-concentrating hormone antagonist useful in the treatment of obesity and other associated or related diseases and conditions.

Accordingly, we have now found a novel group of heterocycles that exhibit a useful profile of activity as antagonists of the melanin-concentrating hormone receptor (MCHR1) disclosed in Nature, Vol. 400, p. 261-265 (1999).

SUMMARY OF THE INVENTION

The present invention provides a compound of formula (I) comprising:



(I)

a pharmaceutically acceptable salt, solvate, or phyisiologically functional derivative thereof, wherein:

(A) is aryl or heteroaryl, optionally substituted one to four times by a least one substiutent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, nitro, and alkylthio groups;

the dashed line connecting Q^2 to Q^3 represents an optional bond;

q, r, s, and t are each independently 0 or 1;

when q is 1, the bond between Q^2 and Q^3 is a double bond;

Q^1 and Q^3 are each independently C or N;

when q is 0 then Q^2 is N, S, or O;

when q is 1, then Q^2 is C or N; when q is 1 and Q^2 is N, then s is 0;

when Q^2 is S or O, s is 0;

when Q^1 is N, r is 0;

when Q^3 is N, t is 0;

R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkylthio;

when Q^1 or Q^3 is C, then each corresponding R^4 is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

when q is 1 and Q^2 is C or when q is 0 and Q^2 is N, then R^5 is selected from hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

Ar is a fused bicyclic ring optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups;

Y is a bond or a C_{1-6} alkylene, optionally substituted;

(i) R^1 and R^2 each independently are selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocycle wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxy, oxo (i.e., =O), alkoxy and halo;

or (ii) R^1 and R^2 may be selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with a substituent selected from halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl;

or (iii) R^1 and R^2 together with the nitrogen atom to which they are bonded form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring, each of said 4-8 membered heterocyclic ring and said 7-11 membered bicyclic heterocyclic ring contain 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, and wherein either said heterocyclic ring or said bicyclic heterocyclic ring may be optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo;

or (iv) R^2 together with the adjacent nitrogen atom and Y may form an optionally substitued nitrogen-containing heterocycle, or R^2 together with the adjacent nitorgen atom, Y, and Ar may form an optionally substitued nitrogen-containing heterocycle or salt thereof, and wherein said heterocycles are optionally substituted one to four times by at least one substituent selected

from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo;

In another aspect of the invention, there is provided a pharmaceutical composition for use in the treatment, prophylaxis or both of one or more conditions or indications set forth herein comprising a compound of formula (I), or a physiologically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient. There is also provided a method of treatment comprising the administration of the above-identified compound of formula (I) to a mammal such as a human, as well as, the use of said compound in the manufacture of a medicine for treating the conditions of obesity, diabetes, depression, and/or anxiety in a mammal (e.g., a human).

In a further embodiment of the invention, there are provided processes for the preparation a compound of formula (I).

Detailed Description of the Invention

As used herein, "a compound of the invention" or "a compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, of physiologically functional derivative (such as, e.g. a prodrug), thereof.

As used herein, unless otherwise specified, the term "alkyl" and "alkylene" refer to straight or branched hydrocarbon chains containing 1 to 6 carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl, tert-butyl, and hexyl. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, and isobutylene. "Alkyl" also includes substituted alkyl. "Alkylene" also includes substituted alkylene. The alkyl and alkylene groups may optionally be substituted with at least one substituent selected from the group consisting of hydroxy, alkoxy, halo, amino, alkylamino, dialkylamino, thio, oxo, aryl, and cyano. Halo, alkoxy, and hydroxy are particularly preferred.

As used herein, unless otherwise specified, the term "cycloalkyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless

otherwise specified) and no carbon-carbon double bonds. "Cycloalkyl" includes by way of example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. "Cycloalkyl" also includes substituted cycloalkyl. The cycloalkyl may be optionally substituted with at least one substituent selected from the group consisting of hydroxy, cyano, halo, alkoxy, amino, alkylamino, dialkylamino, and alkyl. Halo, hydroxy, and alkoxy are preferred.

As used herein, unless otherwise specified, the term "alkenyl" refers to straight or branched hydrocarbon chains containing 2 to 8 carbon atoms and at least one and up to three carbon-carbon double bonds. Examples of "alkenyl" as used herein include, but are not limited to, ethenyl and propenyl. "Alkenyl" also includes substituted alkenyl. The alkenyl group may be optionally substituted with at least one substituent selected from the group consisting of alkyl, amino, alkylamino, dialkylamino, halo, hydroxy, alkoxy, and cyano. Halo, hydroxy, and alkoxy are preferred.

As used herein, unless otherwise specified, the term "cycloalkenyl" refers to a non-aromatic carbocyclic ring having from 3 to 8 carbon atoms (unless otherwise specified) and up to 3 carbon-carbon double bonds. "Cycloalkenyl" includes by way of example, cyclobutenyl, cyclopentenyl, and cyclohexenyl. "Cycloalkenyl" also includes substituted cycloalkenyl. The ring may be optionally substituted with at least one substituent selected from the group consisting of cyano, halo, hydroxy, $-NH_2$, $-N_3$, -CN, $-O-C_{1-3}$ alkyl, $-NH(C_{1-3}$ alkyl), $-N(C_{1-3}$ alkyl$)_2$, and $-C_{1-3}$ alkyl (including haloalkyl).

As used herein, the terms "halo" or "halogen" refer to fluorine, chlorine, bromine, and iodine. Preferred among these are chlorine (or "chloro") and fluorine (or "fluoro").

Unless otherwise specified, the term, "aryl" (as well as "aromatic") refers to monocyclic carbocyclic groups and fused bicyclic carbocylic groups having from 6 to 12 carbon atoms and having at least one aromatic ring. Examples of particular aryl groups include, but are not limited to, phenyl and naphthyl. "Aryl" also includes substituted aryl, especially substituted phenyl. An aryl ring may be optionally substituted with at least one substituent selected from the group consisting of halo, alkyl (including haloalkyl), alkenyl, cycloalkyl, cycloalkenyl, alkoxy, amino, hydroxy, hydroxyalkyl, aminoalkyl,

carboxy, carboxamide, sulfonamide, heteroaryl (abbreviated as "Het"), amidine, cyano, nitro, and azido. Preferred aryl groups according to the invention include, but are not limited to, phenyl and substituted phenyl. Preferred substituted phenyl is a phenyl containing one or more halo groups, particularly chloro and fluoro groups.

The terms "heterocycle" and "heterocyclic" refer to a ring system composed of C and at least one other atom selected from the group consisting of N, O, and S. Heterocycles may or may not be heteroaromatic as defined below. In other words, heteroaromatics are heterocycles, but all heterocycles are not heteroaromatic.

The term "heteroaryl" and "heteroaromatic" refer to a monocyclic or bicylic aromatic ring system composed of C and at least one other atom selected from the group consisting of N, O, and S.

The terms "members" (and variants thereof, e.g., "membered") in the context of heterocyclic, heteroaryl, and aryl groups refers to the total atoms, carbon and heteroatoms (N, O, and/or S) which form the ring. Thus, an example of a 6-membered heterocyclic ring is piperidine, an example of a 6-membered heteroaryl ring is pyridine, and an example of a 6-membered aryl ring is benzene.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and events that do not occur.

Formula (I) of the invention is set forth in detail as follows.


is aryl or heteroaryl, optionally substituted one to four times with at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, nitro, and alkylthio groups. Preferred among these substituted groups are halo, C_{1-3} alkyl, and C_{1-3} alkoxy. Most preferred are fluoro, chloro, and methoxy. In a preferred embodiment said  is substituted with a halo group, q is 0, Q^1 is carbon, Q^2 is sulfur, and R^4 is

hydrogen or halo. For example,  is 4-chlorophenyl and R^3 and R^4 are each hydrogen.

In the formula, the dashed line connecting Q^2 to Q^3 represents an optional bond such that the bond between Q^2 and Q^3 are connected by a double bond; and q, r, s, and t are each independently 0 or 1.

In formula (I), q is 0 or 1. When q is 1 the bond between Q^2 and Q^3 in formula (I) is a double bond. When q is 0 there is no Q^3 group. When q is 0 then Q^2 is N, S, or O. And when q is 1, Q^2 is C or N. When q is 1 and Q^2 is N, then s is 0 and there is no R^5 substituent.

Q^1 and Q^3 are each independently carbon (C) or nitrogen (N). In one embodiment, Q^1, Q^2, and Q^3 are each carbon and q, r, s, and t are 1. In another embodiment, Q^1 is carbon, Q^2 is sulfur, q and s are 0, and r is 1.

In the formula, r and t are each independently 0 or 1. When r and t are each independently 0, then there is no R^4 substituent. When r and t are each independently 1, Q^1 and Q^3 are each independently bonded by the group R^4. Each R^4 is the same or different and is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamio, hydroxy, cyano, alkylthio, and halo.

In formula (I), s is 0 or 1. When Q^2 is S or O, then s is 0 and there is no R^5 group. When Q^2 is C, then s is 1 and R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo. When Q^2 is C, preferably R^5 is hydrogen or a C_{1-3} alkyl; most preferably R^5 is hydrogen or methyl.

In formula (I), R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, and C_{3-6} cycloalkyl. Preferably, R^3 is hydrogen or a C_{1-3} alkyl; most preferably R^3 is hydrogen or methyl.

When either or both Q^1 and Q^3 are C, then R^4 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo. Preferably, when either or both Q^1 and Q^3 are C, R^4 is hydrogen or C_{1-3} alkyl; most preferably R^4 is hydrogen or methyl.

When Q^2 is N, and s is 1, R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkyl amino, hydroxy, cyano, alkylthio, and halo. When Q^2 is N, and s is 1, preferably R^5 is hydrogen or a C_{1-3} alkyl; most preferably R^5 is hydrogen or methyl.

In the formula (I), Ar is an optionally substituted fused bicyclic ring having 9 to 14 members, optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, and alkylthio groups. That is, Ar can be a fused bicyclic ring having: (i) two aromatic rings fused together, (ii) an aromatic ring and a heteroaromatic ring fused together, (iii) two heteroaromatic rings fused together, (iv) an aromatic ring fused to a heterocyclic ring, or (v) having an aromatic ring fused to a carbocyclic ring. Preferably, Ar is selected from the group consisting of quinoline, naphthalene, benzimidazole, indole, benzothiophene, benzofuran, and benzothiazole. When Ar is a ten-membered bicyclic aromatic or ten-membered bicyclic heteroaromatic ring, then preferably Ar is quinoline or naphthalene. When Ar is a 9-membered fused bicyclic heteroaromatic ring, then preferably Ar is benzimidazole, indole, benzothiophene, benzofuran, or benzothiazole.

In the formula (I), Y is a bond or a C_{1-6} alkylene, optionally substituted as defined herein. When Ar is a ten-membered polycyclic aromatic or ten-membered polycyclic heteroaromatic ring, then preferably Y is a C_{1-3} alkylene, optionally substituted; most preferably Y is methylene ($-CH_2-$), optionally substituted. When Ar is a 9-membered fused polycyclic heteroaromatic ring, then preferably Y is a bond or a C_{1-3} alkylene, optionally substituted; most preferably Y is a bond.

In (i), R^1 and R^2 of formula (I) are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, phenyl, and 5- or 6-membered heterocycle, wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, hydroxy, oxo, alkoxy, and halo.

Preferably, R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} cycloalkyl. Most preferably, R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-3} alkyl, and C_{3-6} cycloalkyl.

Or, in (ii), R^1 and R^2 are selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with at least one substituent selected from the group consisting of halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl. Preferably, when either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is a hydrogen, a C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

Additionally, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded can form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring. The 4-8 membered heterocyclic ring and/or the 7-11 membered bicyclic heterocyclic ring may contain 1, 2, or 3 heteroatoms selected from the group consisting of N, O, and S. And either the heterocyclic ring or the bicyclic heterocyclic ring may be optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, oxo, and halo. Here neither group R^1 or R^2 is linked to M or L. Preferably, R^1 and R^2 together form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicylic heterocyclic ring, having 1 or 2 heteroatoms selected from the group N, O, and S wherein said heterocyclic ring and said bicyclic heterocyclic ring may be optionally substituted up to two times with a substituent selected from the group consisting of oxo and halo.

Also additionally, in (iv), R^2 together with the adjacent nitrogen atom and Y may form an optionally substituted nitrogen-containing heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogen-containing heterocycle or salt thereof. The said nitrogen-containing heterocycles are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl,

hydroxy, C_{1-3} alkoxy, oxo (i.e., =O), amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo. Preferably, R^2 together with the adjacent nitrogen atom and Y form a 3-7 membered ring when Y is a C_{1-6} alkyl group. Most preferably a 5-7 membered ring is formed. The 5-7 membered ring is optionally substituted by at least one substitutent selected from the group consisting of phenyl, one to four C_{1-3} alkyl, hydroxy, alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, or halo.

In one embodiment, when Ar is a 10-membered aromatic ring or a 10-membered heteroaromatic ring, the most preferred compounds according to this invention are selected from the group consisting of

6-(4-chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one;

6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one;

6-(4-fluorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2-methyl-4,5-dihydro-1*H*-imidazol-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

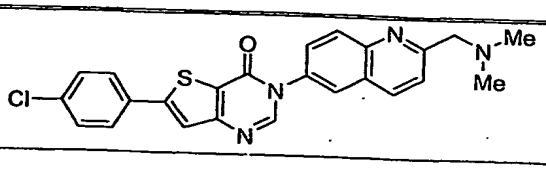
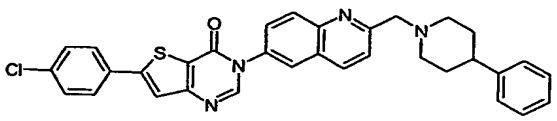
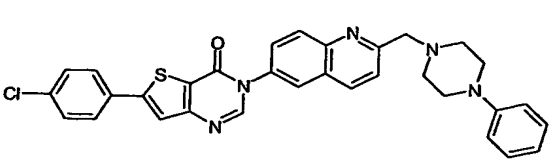
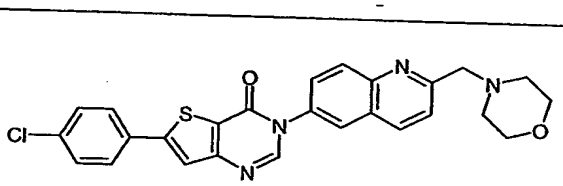
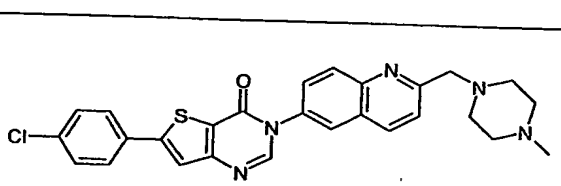
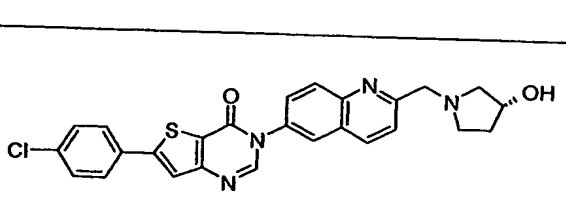
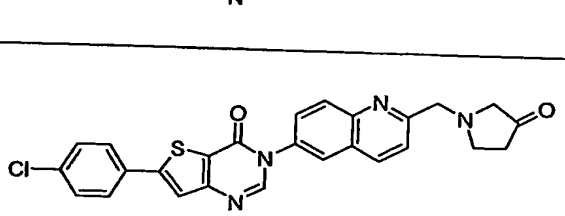
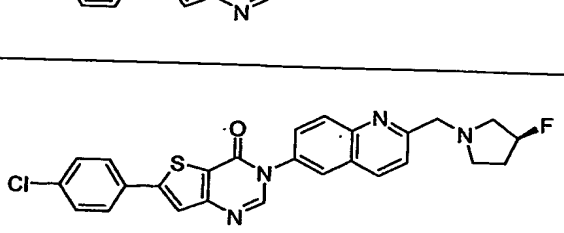
6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

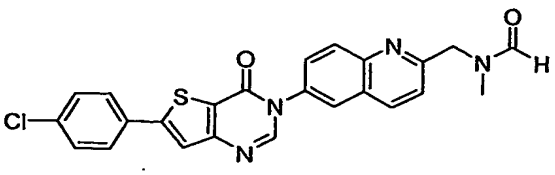
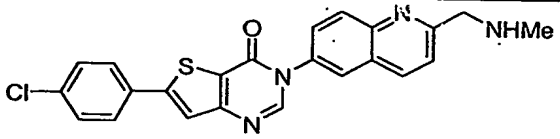
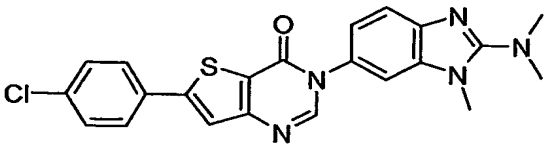
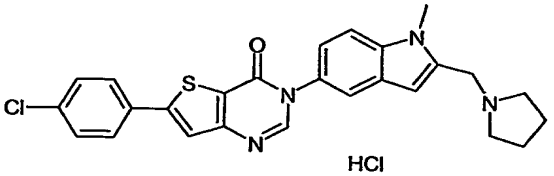
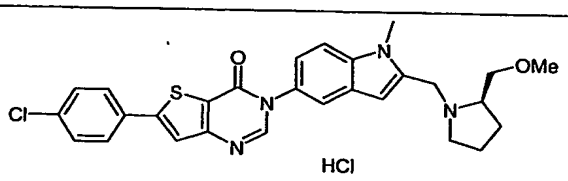
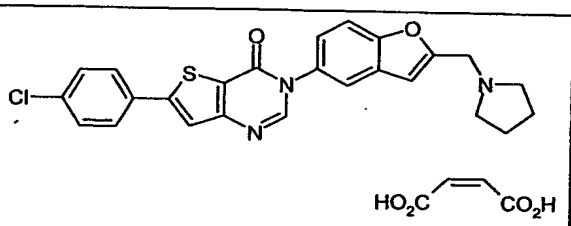
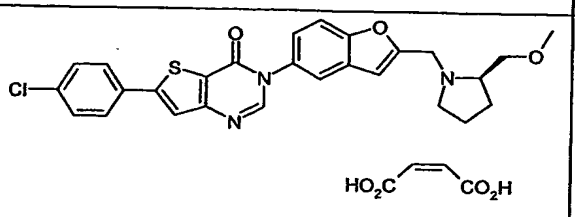
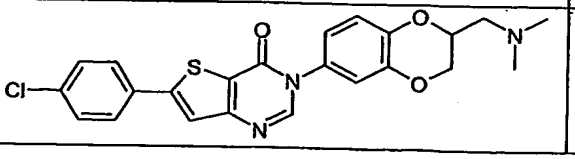
In another embodiment, when Ar is a 9-membered heteroaromatic ring, the most preferred compound according to this invention is 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

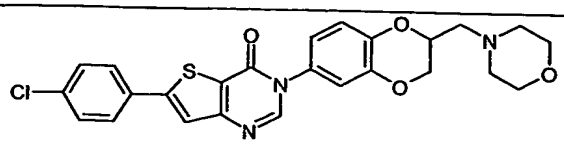
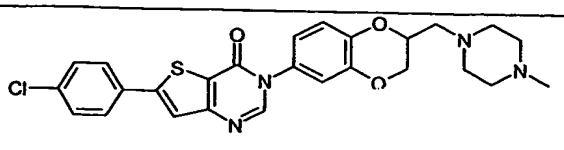
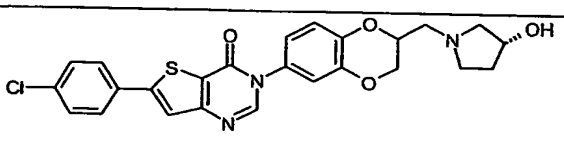
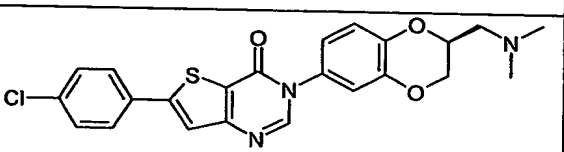
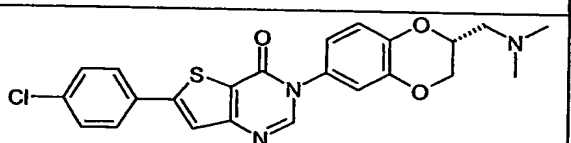
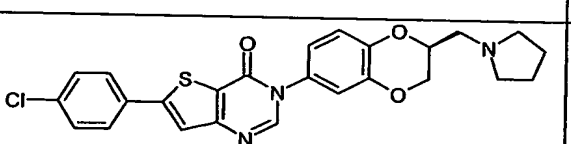
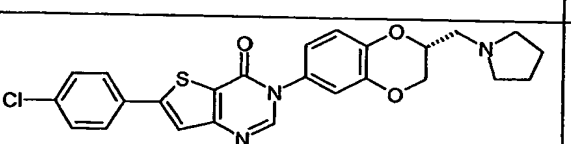
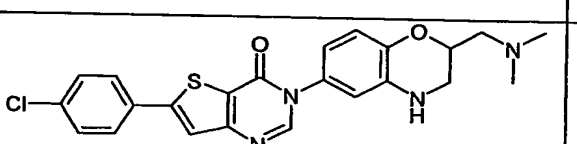
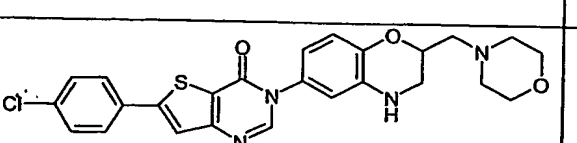
Certain compounds of formula (I) may exist in stereoisomeric forms (e.g., they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centers are inverted. Certain compounds of formula (I) may be prepared as regioisomers. The present invention covers both the mixture of regioisomers as well as individual compounds. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

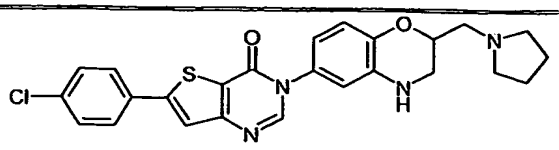
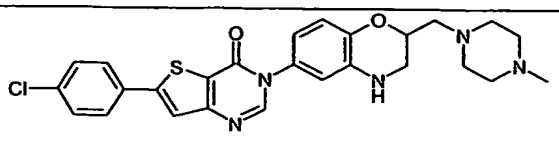
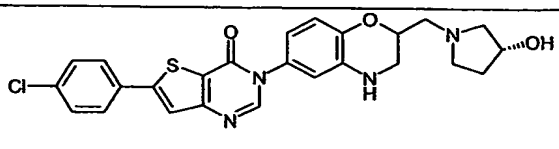
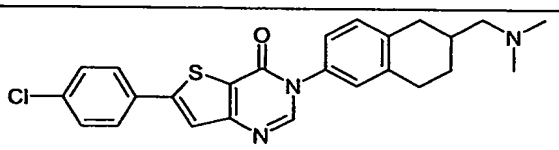
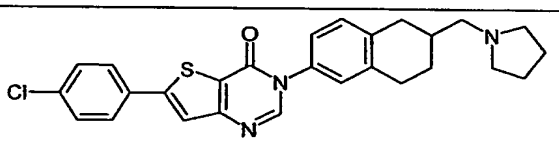
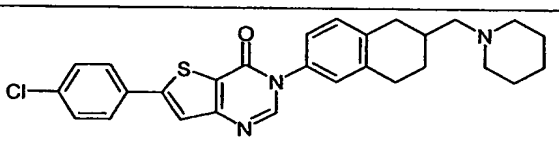
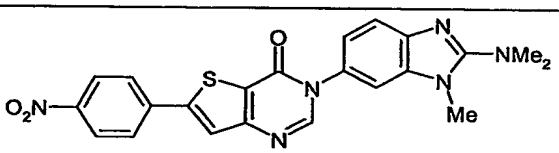
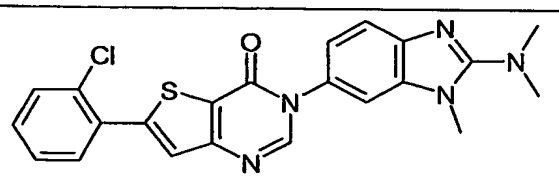
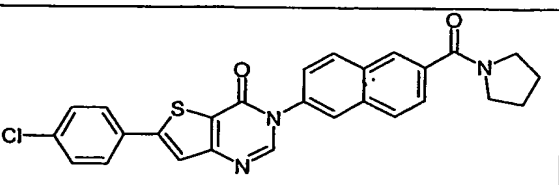
It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove. Specific compounds of formula (I) include but are not limited those set forth in Table I and/or those prepared examples herein.

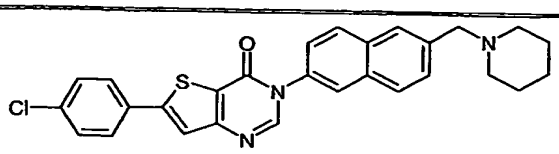
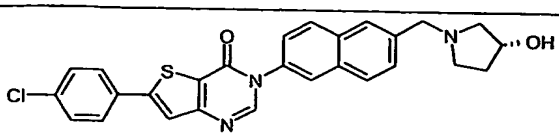
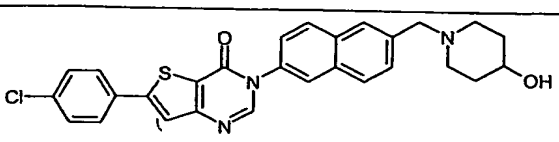
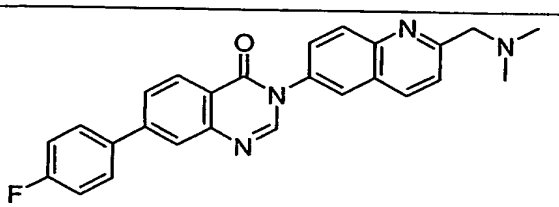
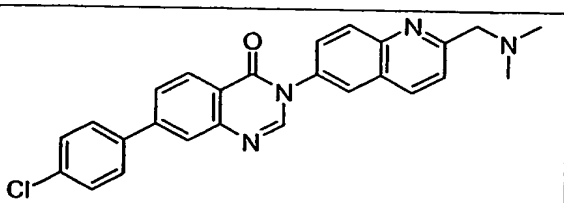
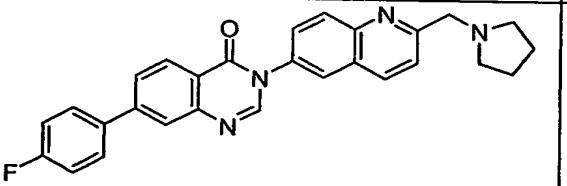
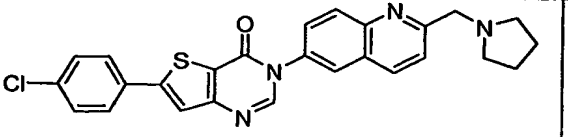
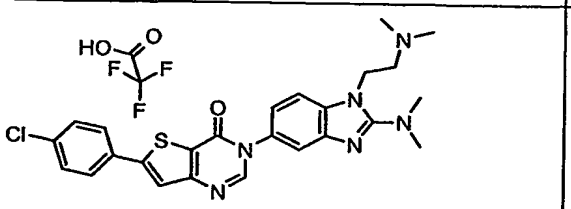
Table I

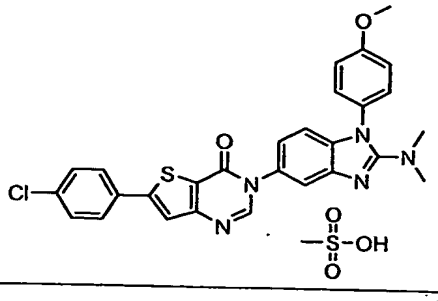
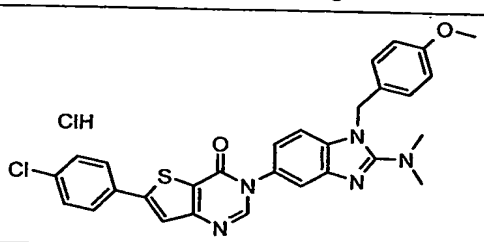
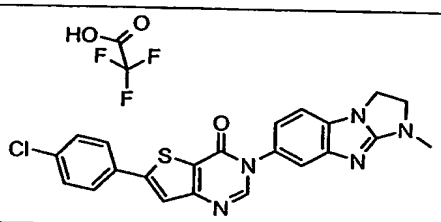
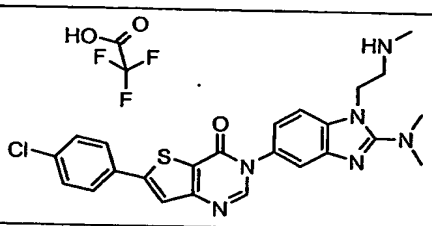
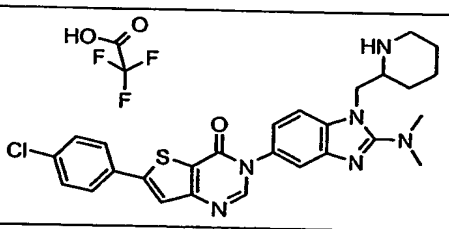
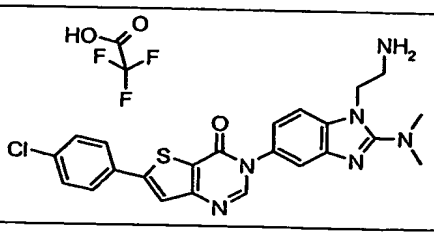
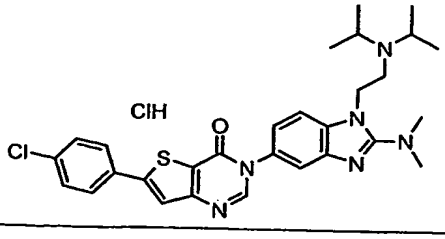
Example No.	Structure	Name
1		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
2		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
3		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
4		6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
5		6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
6		3-[2-(hydroxymethyl)-6-quinolinyl]-6(4-methylphenyl)thieno[3,2-d]pyrimidin-4(3H)one
7		6-(4-chlorophenyl)-3-{2-[(3-oxo-1-pyrrolidinyl)methyl]-6-quinolinyl}thieno[3,2-d]pyrimidin-4(3H)-one
8		6-(4-chlorophenyl)-3-(2-{[(3S)-3-fluoropyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-d]pyrimidin-4(3H)-one

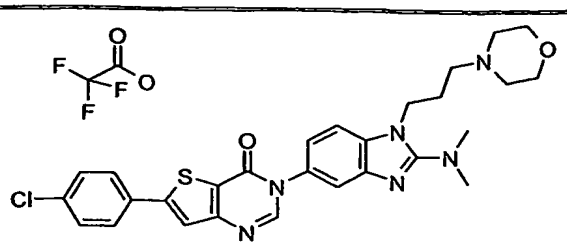
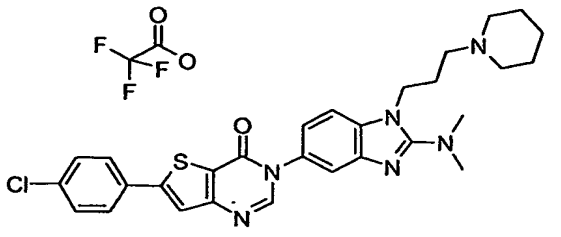
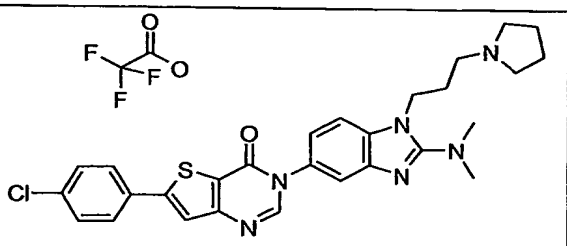
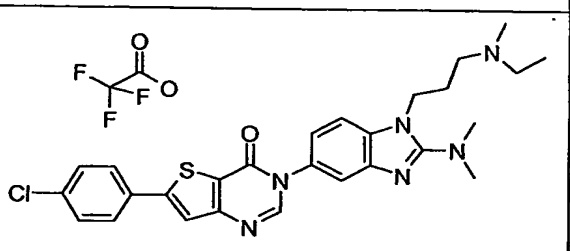
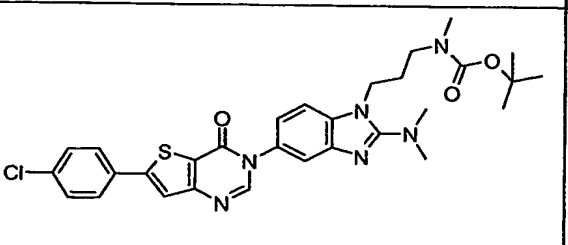
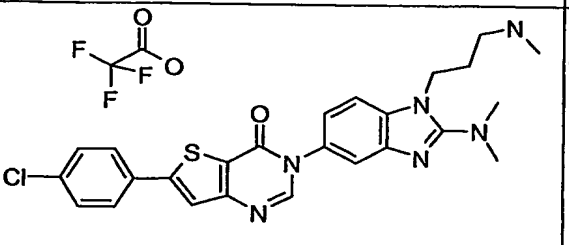
Example No.	Structure	Name
9		[6-(6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl)-2-quinolinyl]methyl(methyl)-formamide
10		6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
11		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
12		6-(4-chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1H-indol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride
13		6-(4-chlorophenyl)-3-(2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-1-methyl-1H-indol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride
14		6-(4-methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one maleate salt
15		3-(2-{[(2R)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-1-benzofuran-5-yl)-6-(4-methylphenyl)thieno[3,2-d]pyrimidin-4(3H)-one maleate salt
16		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-

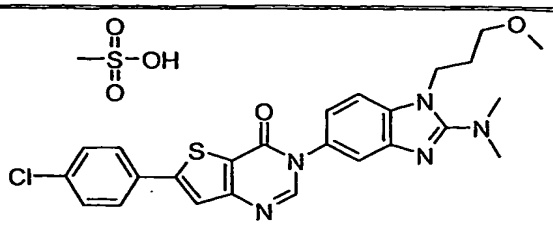
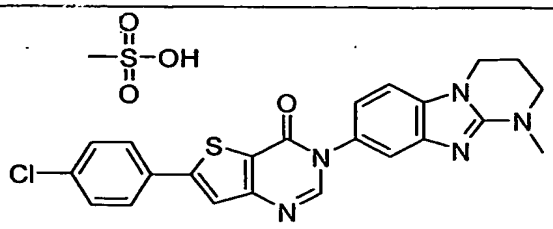
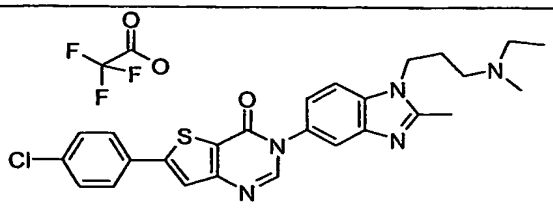
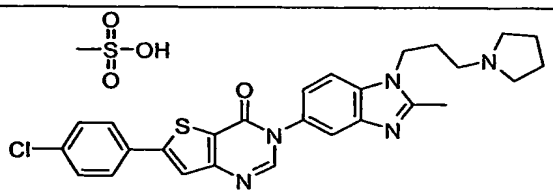
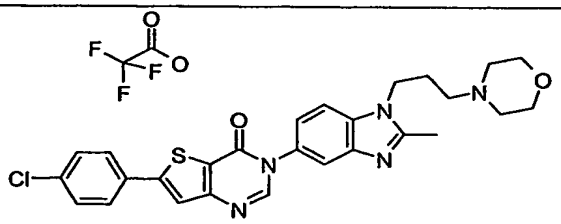
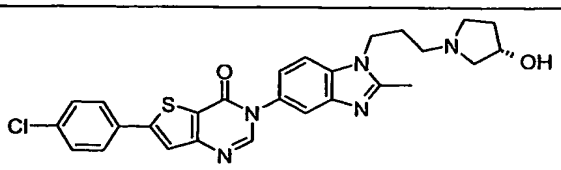
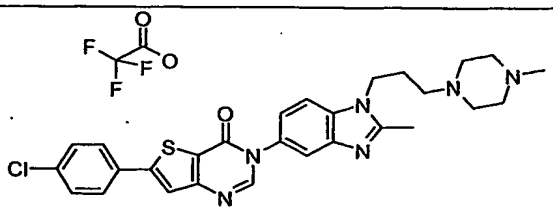
Example No.	Structure	Name
		one
17		6-(4-chlorophenyl)-3-[2-(4-morpholinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
18		6-(4-chlorophenyl)-3-{2-[(4-methyl-1-piperazinyl)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
19		6-(4-chlorophenyl)-3-(2-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one
20		6-(4-chlorophenyl)-3-{(2S)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
21		6-(4-chlorophenyl)-3-{(2R)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
22		6-(4-chlorophenyl)-3-[(2S)-2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
23		6-(4-chlorophenyl)-3-[(2R)-2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
24		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
25		6-(4-chlorophenyl)-3-[2-(4-morpholinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one

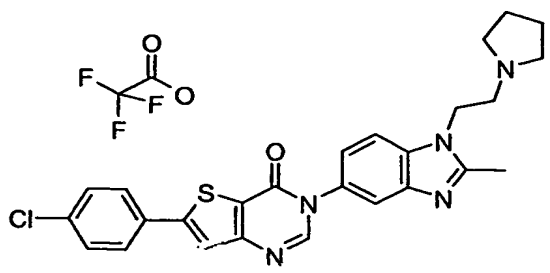
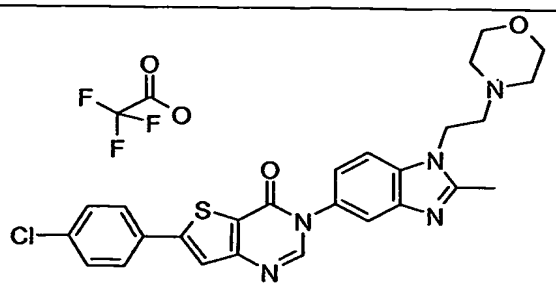
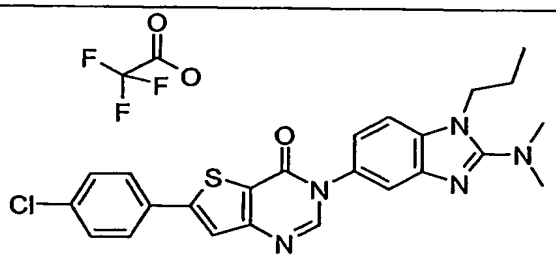
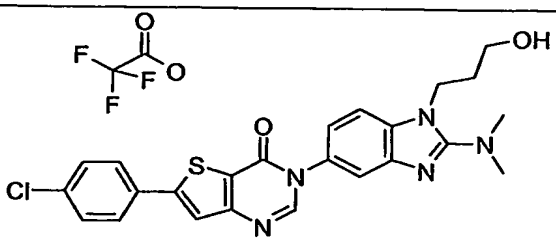
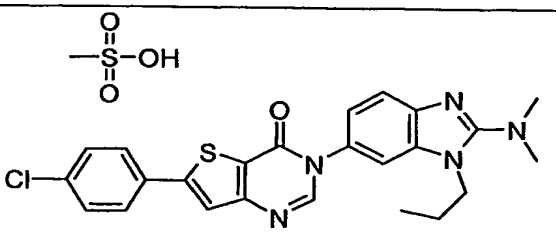
Example No.	Structure	Name
26		6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
27		6-(4-chlorophenyl)-3-{2-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one
28		6-(4-chlorophenyl)-3-(2-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}-3,4-dihydro-2H-1,4-benzoxazin-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one
29		6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one
30		6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one
31		6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one
32		3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]-6-(4-nitrophenyl)thieno[3,2-d]pyrimidin-4(3H)-one
33		6-(2-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
34		6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylcarbonyl)-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one

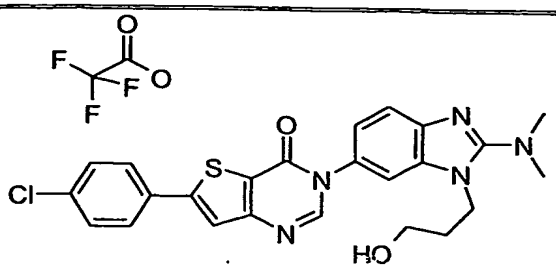
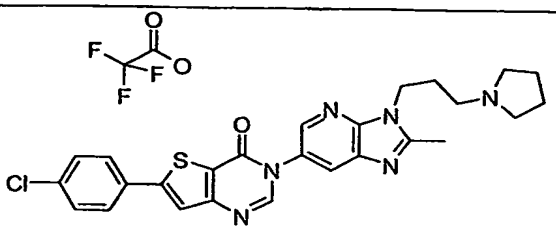
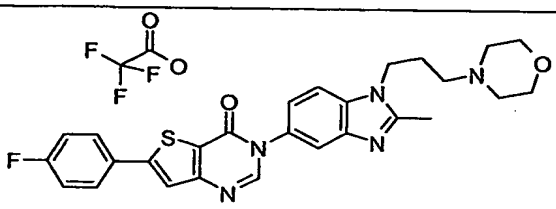
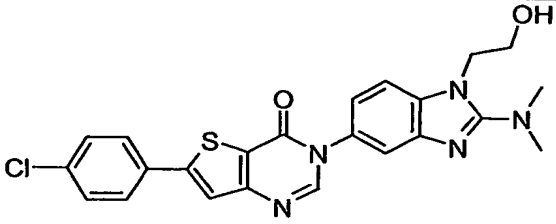
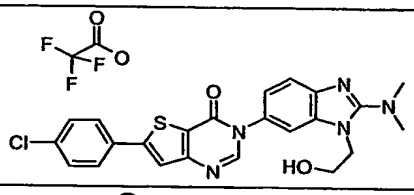
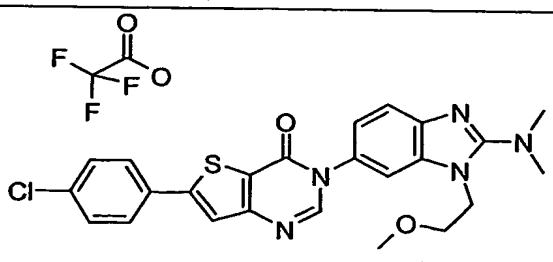
Example No.	Structure	Name
35		6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one
36		6-(4-chlorophenyl)-3-(6-{[(3R)-3-hydroxy-1-pyrrolidinyl]methyl}-2-naphthalenyl)thieno[3,2-d]pyrimidin-4(3H)-one
37		6-(4-chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one
38		3-{2-[(dimethylamino)methyl]-6-quinolinyl}-7-(4-fluorophenyl)-4(3H)-quinazolinone
39		7-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-6-quinolinyl}-4(3H)-quinazolinone
40		7-(4-fluorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]-4(3H)-quinazolinone
41		6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]thieno[3,2-d]pyrimidin-4(3H)-one
42		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

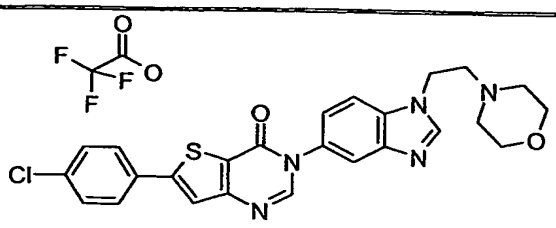
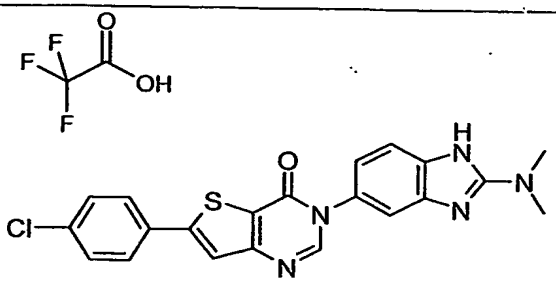
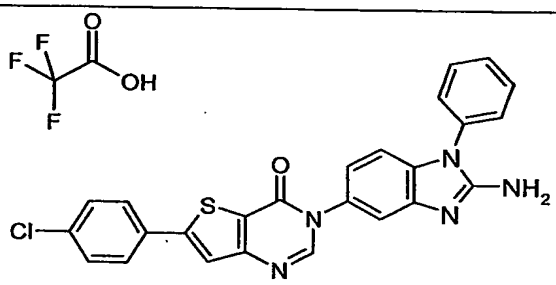
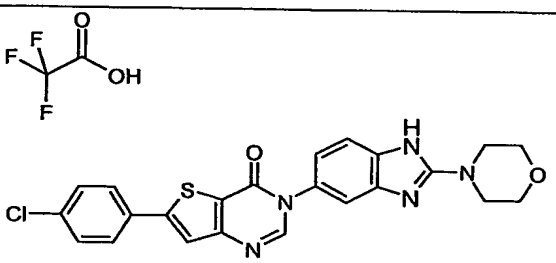
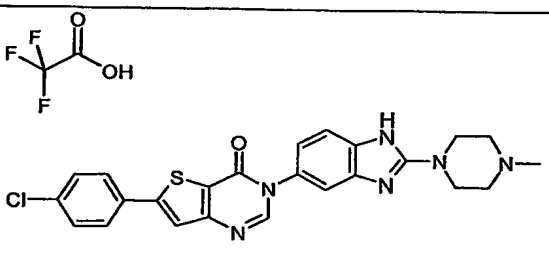
Example No.	Structure	Name
43		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[4-(methyloxy)phenyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
44		6-(4-chlorophenyl)-3-(2-(dimethylamino)-1-{[4-(methyloxy)phenyl]methyl}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride
45		6-(4-chlorophenyl)-3-(1-methyl-2,3-dihydro-1H-imidazo[1,2-a]benzimidazol-7-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
46		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methylamino)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
47		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-piperidinylmethyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
48		3-[1-(2-aminoethyl)-2-(dimethylamino)-1H-benzimidazol-5-yl]-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
49		3-[1-{2-[bis(1-methylethyl)amino]ethyl}-2-(dimethylamino)-1H-benzimidazol-5-yl]-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one hydrochloride

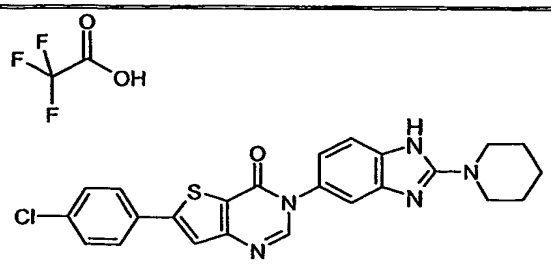
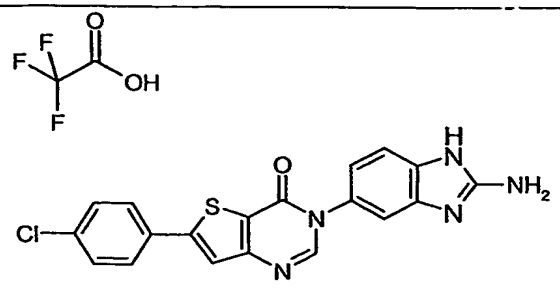
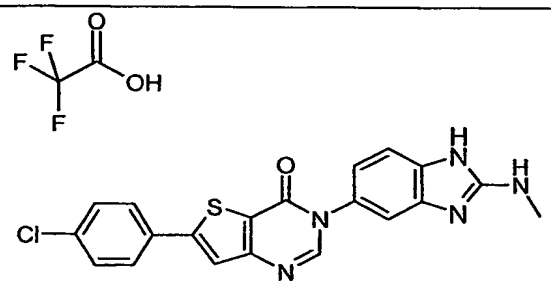
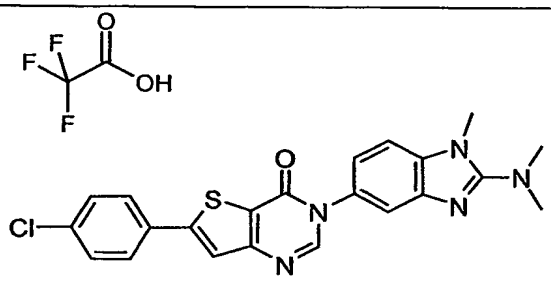
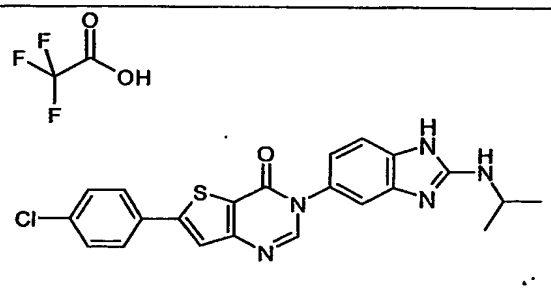
Example No.	Structure	Name
50		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-morpholin-4-ylpropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
51		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-piperidin-1-ylpropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
52		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-pyrrolidin-1-ylpropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
53		6-(4-chlorophenyl)-3-(2-(dimethylamino)-1-{3-[ethyl(methyl)amino]propyl}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
54		tert-butyl {3-[5-[6-(4-chlorophenyl)-4-oxothieno[3,2-d]pyrimidin-3(4H)-yl]-2-(dimethylamino)-1H-benzimidazol-1-yl]propyl}methylcarbamate
55		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[3-(methylamino)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

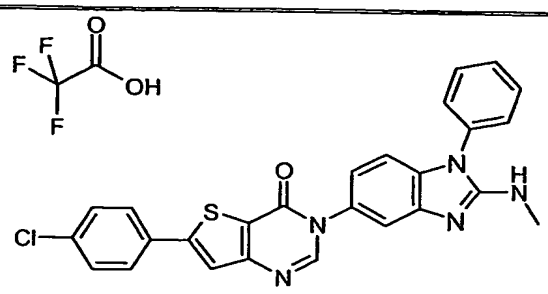
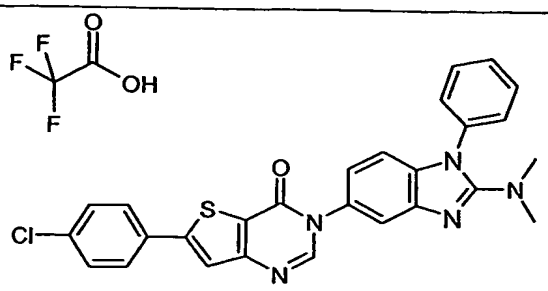
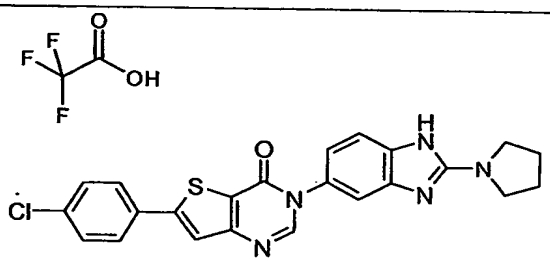
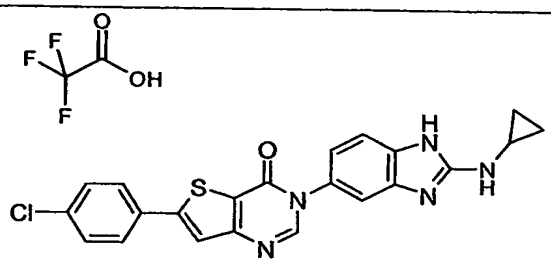
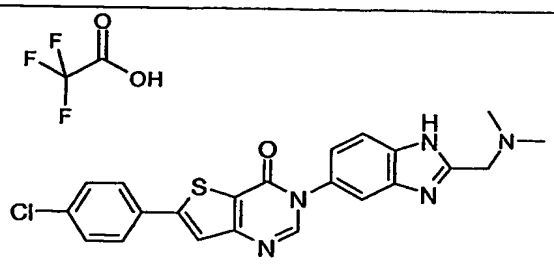
Example No.	Structure	Name
56		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-methoxypropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
57		6-(4-chlorophenyl)-3-(1-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazol-8-yl)thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
58		6-(4-chlorophenyl)-3-(1-{3-[ethyl(methyl)amino]propyl}-2-methyl-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
59		6-(4-chlorophenyl)-3-{2-methyl-1-[3-(1-pyrrolidinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
60		6-(4-chlorophenyl)-3-{2-methyl-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
61		6-(4-chlorophenyl)-3-(1-{3-[(3S)-3-hydroxy-1-pyrrolidinyl]propyl}-2-methyl-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one
62		6-(4-chlorophenyl)-3-{2-methyl-1-[3-(4-methyl-1-piperazinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

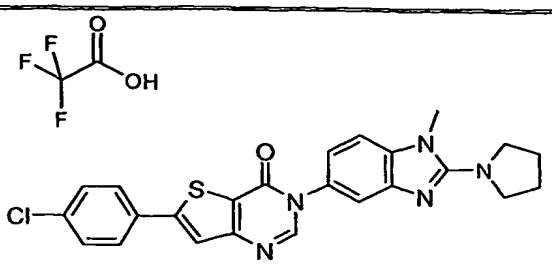
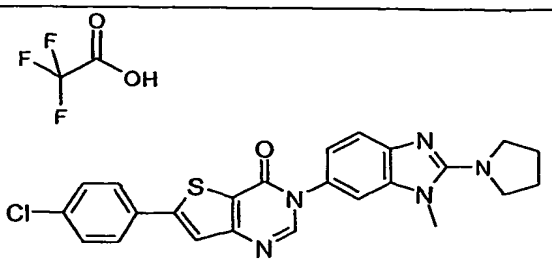
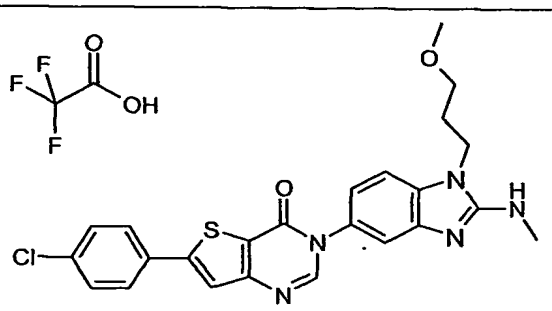
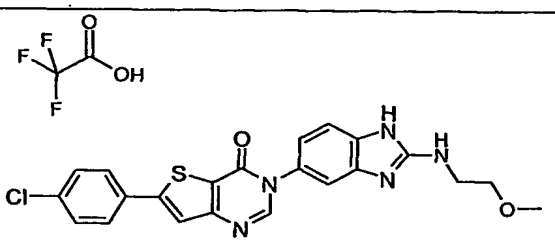
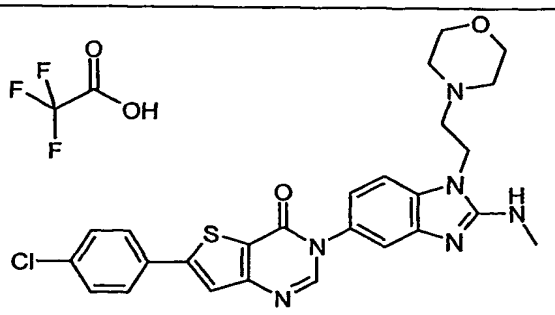
Example No.	Structure	Name
63		methyl-1-[2-(1-pyrrolidinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
64		6-(4-chlorophenyl)-3-{2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
65		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
66		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate (salt)
67		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate

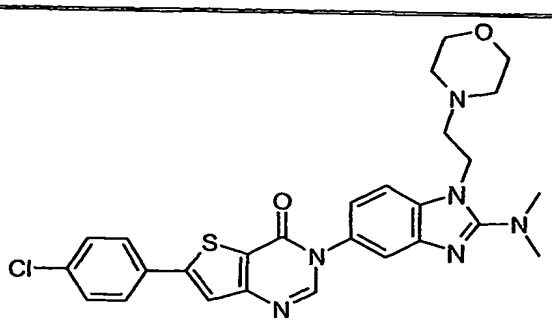
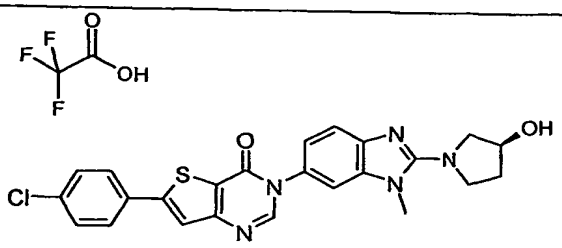
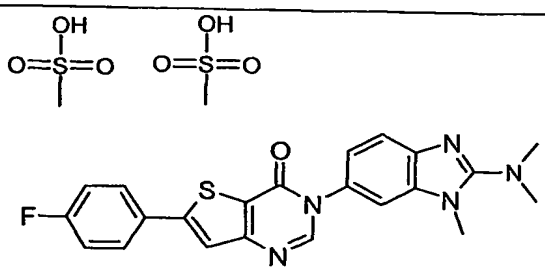
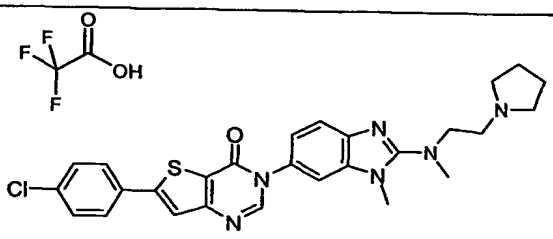
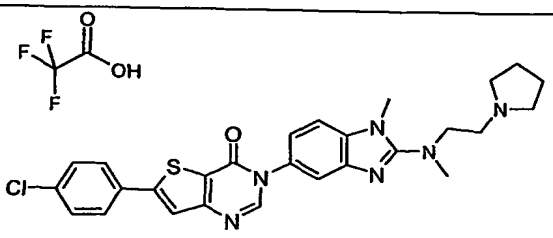
Example No.	Structure	Name
68		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate (salt)
69		6-(4-chlorophenyl)-3-{2-methyl-3-[3-(1-pyrrolidinyl)propyl]-3H-imidazo[4,5-b]pyridin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
70		6-(4-fluorophenyl)-3-{2-methyl-1-[3-(4-morpholinyl)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
71		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one
72		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
73		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methyloxy)ethyl]-1H-benzimidazol-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

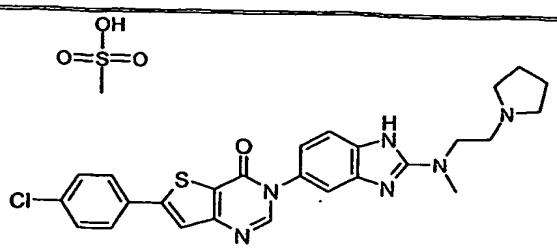
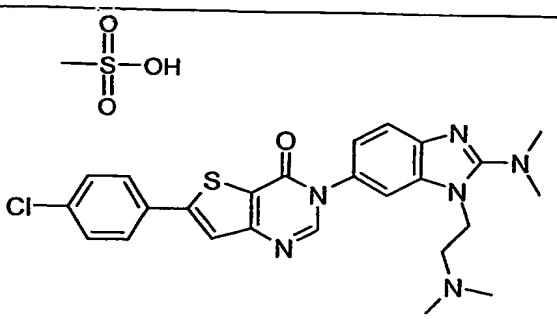
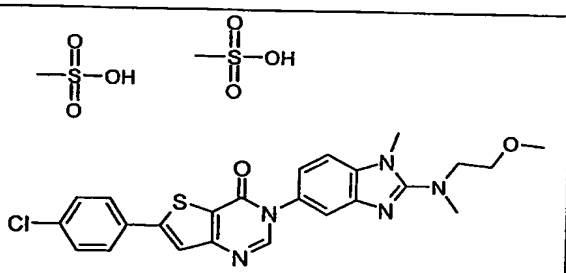
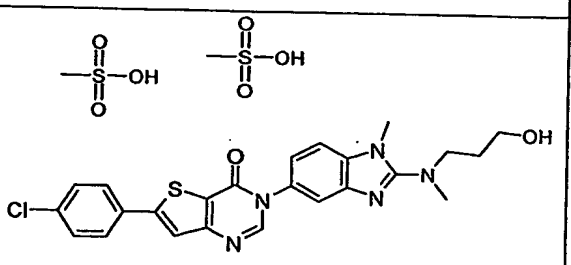
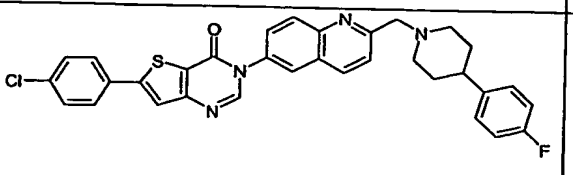
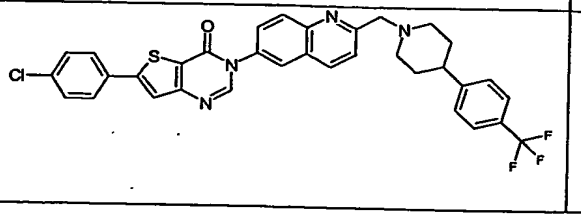
Example No.	Structure	Name
74		6-(4-chlorophenyl)-3-{1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
75		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
76		3-(2-amino-1-phenyl-1H-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
77		6-(4-chlorophenyl)-3-[2-(4-morpholinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
78		6-(4-chlorophenyl)-3-[2-(4-methyl-1-piperazinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

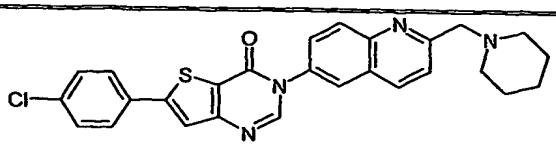
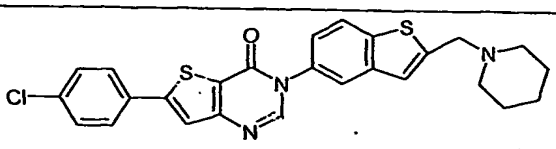
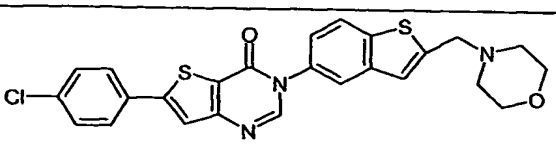
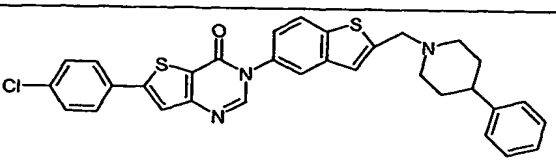
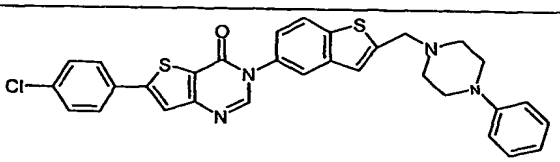
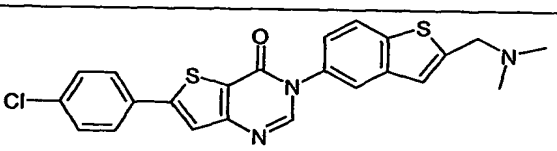
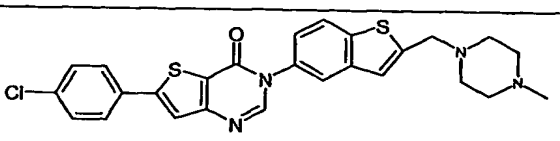
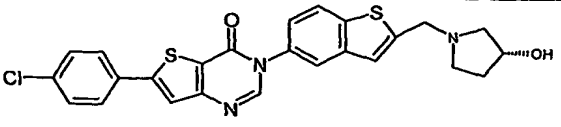
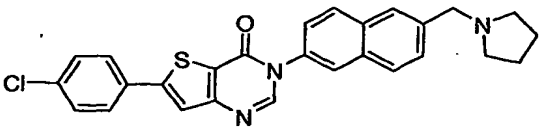
Example No.	Structure	Name
79		6-(4-chlorophenyl)-3-[2-(1-piperidinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
80		3-(2-amino-1H-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
81		6-(4-chlorophenyl)-3-[2-(methylamino)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
82		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
83		6-(4-chlorophenyl)-3-{2-[(1-methylethyl)amino]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

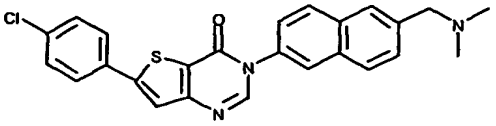
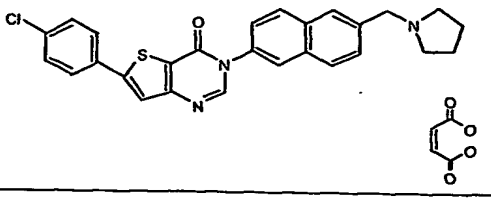
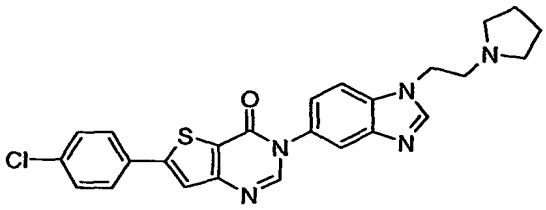
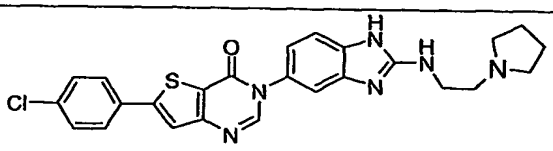
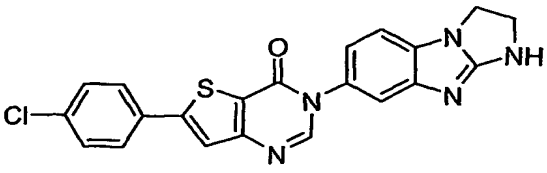
Example No.	Structure	Name
84		6-(4-chlorophenyl)-3-[2-(methylamino)-1-phenyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
85		6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-phenyl-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
86		6-(4-chlorophenyl)-3-[2-(1-pyrrolidinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
87		6-(4-chlorophenyl)-3-[2-(cyclopropylamino)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
88		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

Example No.	Structure	Name
89		6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1H-benzimidazol-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
90		6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1H-benzimidazol-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
91		6-(4-chlorophenyl)-3-{2-(methylamino)-1-[3-(methyloxy)propyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
92		6-(4-chlorophenyl)-3-(2-{[2-(methyloxy)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
93		6-(4-chlorophenyl)-3-{2-(methylamino)-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

Example No.	Structure	Name
94		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(4-morpholinyl)ethyl]-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
95		6-(4-chlorophenyl)-3-{2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-methyl-1H-benzimidazol-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate (salt)
96		3-[2-(dimethylamino)-1-methyl-1H-benzimidazol-6-yl]-6-(4-fluorophenyl)thieno[3,2-d]pyrimidin-4(3H)-one dimethanesulfonate
97		6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1H-benzimidazol-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate
98		6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one trifluoroacetate

Example No.	Structure	Name
99		6-(4-chlorophenyl)-3-(2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
100		6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1H-benzimidazol-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one methanesulfonate
101		6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(methyloxy)ethyl]amino}-1H-benzimidazol-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one dimethanesulfonate
102		6-(4-chlorophenyl)-3-{2-[(3-hydroxypropyl)(methyl)amino]-1-methyl-1H-benzimidazol-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one dimethanesulfonate
103		6-(4-chlorophenyl)-3-(2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-yl)thieno[3,2-d]pyrimidin-4(3H)-one
104		6-(4-chlorophenyl)-3-[2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one

Example No.	Structure	Name
105		6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one
106		6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)-1-benzothien-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one
107		6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)-1-benzothien-5-yl]thieno[3,2-d]pyrimidin-4(3H)-one
108		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
109		6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
110		6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
111		6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one
112		6-(4-chlorophenyl)-3-(2-{[(3R)-3-hydroxypyrrolidin-1-yl]methyl}-1-benzothien-5-yl)thieno[3,2-d]pyrimidin-4(3H)-one
113		6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-d]pyrimidin-4(3H)-one

Example No.	Structure	Name
114		6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one
115		6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-2-naphthalenyl]thieno[3,2-d]pyrimidin-4(3H)-one maleate salt
116		6-(4-chlorophenyl)-3-{1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one
117		6-(4-chlorophenyl)-3-(2-{[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one
118		6-(4-chlorophenyl)-3-(2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

It will be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate or physiologically functional derivative thereof (e.g., a prodrug). The pharmaceutically acceptable salts of the compounds of

formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium salts. More specific examples of suitable acid salts include maleic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, aleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic (mesylate), naphthaliene-2-sulfonic, benzenesulfonic, hydroxynaphthoic, hydroiodic, malic, steroic, tannic, and the like.

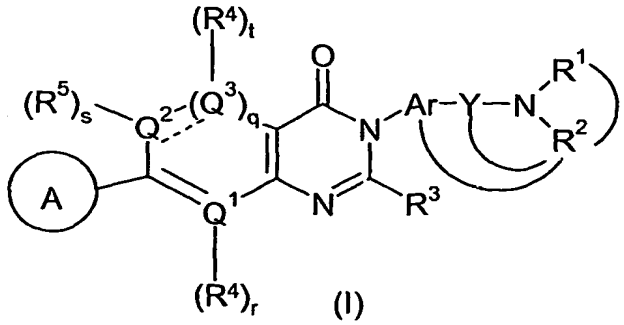
Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminum, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts.

The term "solvate" as used herein refers to a complex of variable stoichiometry formed by a solute (a compound of formula (I)) and a solvent. Solvents, by way of example, include water, methanol, ethanol, and acetic acid.

The term "physiologically functional derivative" as used herein refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, a ester or an amide of a compound of formula (I), which upon administration to an animal, particularly a mammal, such as a human, is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. See, for example, Burger's Medicinal Chemistry and Drug Discovery, 5th Edition, Vol. 1: Principles and Practice.

Processes for preparing pharmaceutically salts, solvates, and physiologically functional derivatives of the compounds of formula (I) are conventional in the art. See, e.g., Burger's Medicinal Chemistry and Drug Discovery,5th Edition, Vol.1: Principles and Practice.

Compounds of formula (I) below are conveniently prepared in accordance with the reaction schemes and/or processes outlined or described herein.

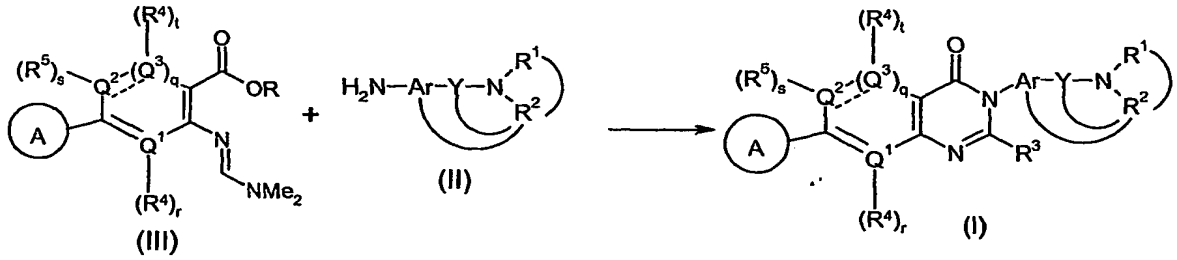


(I)

As will be apparent to those skilled in the art, in the processes described below for the preparation of compounds of formula (I), certain intermediates, may be in the form of pharmaceutically salts, solvates or physiologically functional derivatives of the compound. With respect to any intermediate employed in the process of preparing compounds of formula (I), the terms or identifiers have the same meanings as noted above with respect to compounds of formula (I). In general, processes for preparing pharmaceutically acceptable salts, solvates and physiologically functional derivatives of intermediates are known, and the process for preparing pharmaceutically acceptable salts, solvates and physiological functional derivatives of the compounds of formula (I) are similar and set forth below.

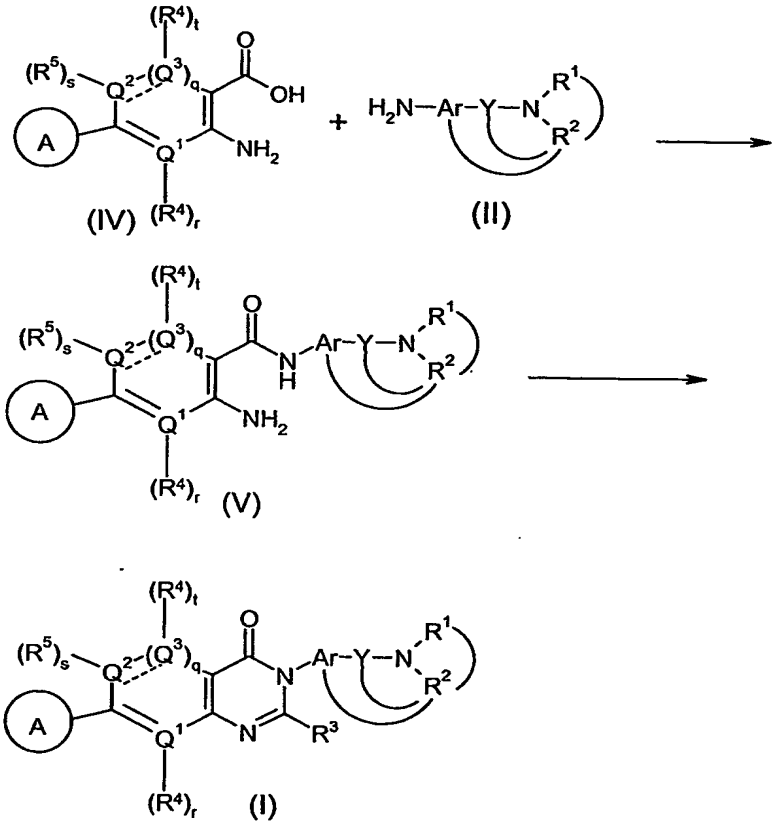
Unless otherwise stated,  , R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t are as defined in formula (I) for all of the processes enumerated herein.

Thus, compounds of formula (I) wherein R^5 is H may be prepared by reaction of an aniline of formula (II) with a formamidine ester of formula (III) wherein R is C_{1-4} alkyl.

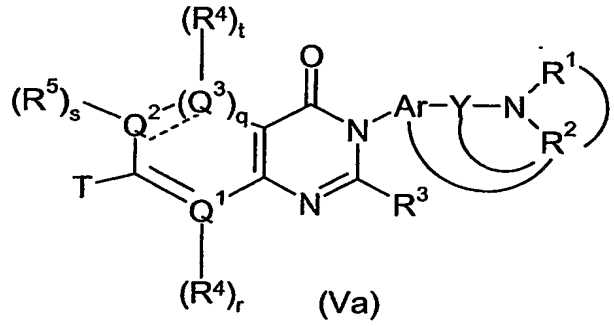


(III) (II) (I)

Compounds of formula (I) can also be prepared by an amide coupling of the corresponding amino acid (IV) and the desired aniline (II) in a solvent, such as methylene chloride, with amide coupling agents such as EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride), followed by cyclization in refluxing carboxylic acids, such as formic acid.



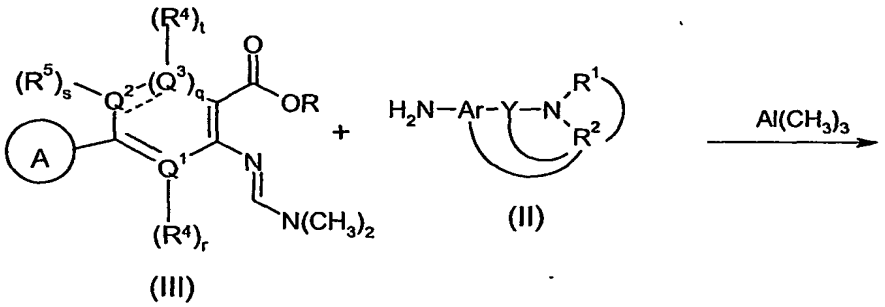
Compounds of formula (I) may also be prepared by reaction of a compound of formula (Va)



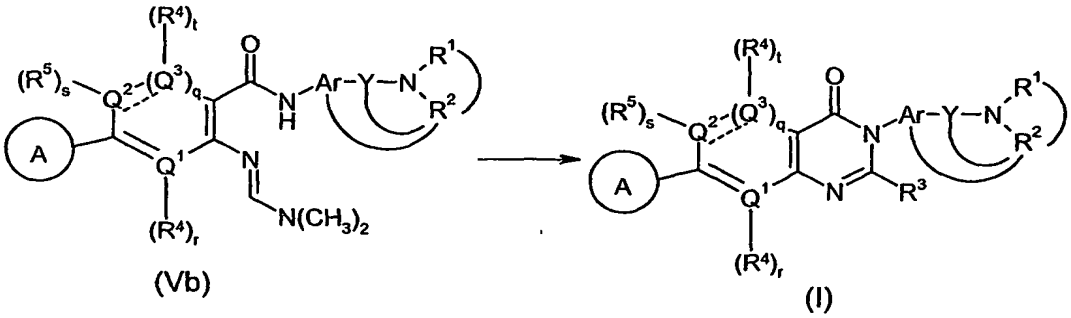
with a compound capable of introducing the group (A), and T is a leaving group (e.g., chloro, bromo, iodo, and triflate (-OSO_2CF_3)).

Thus compounds of formula (I) may be prepared from the compound of formula (Va) with a boronic acid and a palladium catalyst using a Suzuki coupling reaction or with an organostannane reagent and a palladium catalyst using a Stille coupling reaction.

Compounds of formula (I) may also be prepared by reaction of an amino ester of formula (III) wherein R is C_{1-4} alkyl with an aniline of formula (II) in a solvent such as dichloromethane or 1,2-dichloroethane in the presence of trimethylaluminum to produce a compound of formula (Vb) and cyclizing said compound of formula (Vb).

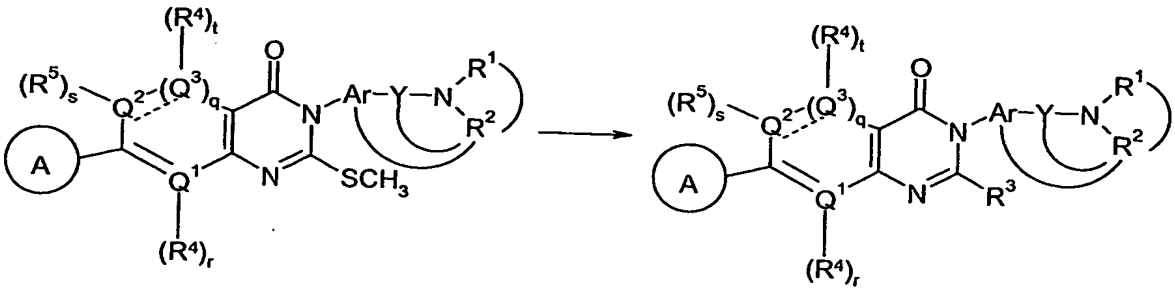


(III) (II)



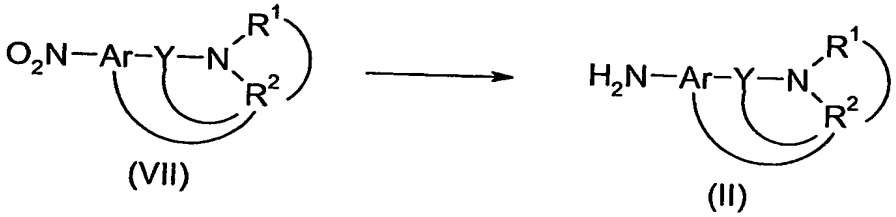
(Vb) (I)

Compounds of formula (I) wherein R^3 is hydrogen may also be prepared by reaction of a sulfur-containing compound such as (VI) with a reductant, such as Raney Nickel, in a solvent such as ethanol.



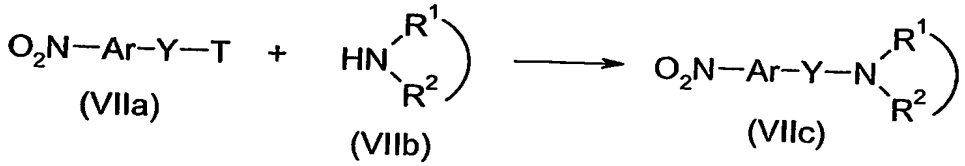
(VI) (I)

Compounds of formula (II) may be prepared by reduction of the corresponding nitroaromatic (VII) using hydrogen and a catalyst (e.g., 10% Pd on carbon), stannous chloride, or sodium dithionite.



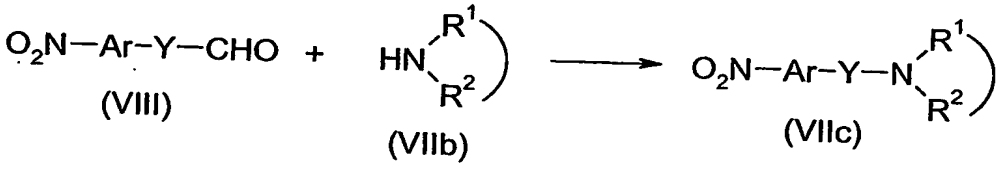
(VII) (II)

Compounds of formula VIIc wherein Y is CH_2 can be prepared from a compound (VIIa) and an amine (VIIb) and T is a leaving group (e.g., Cl, Br, I, mesylate, and tosylate).



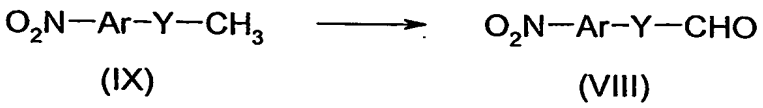
(VIIa) (VIIb) (VIIc)

Alternatively, compounds of this type can be made by reductive amination of an aldehyde of formula (VIII) by an amine of formula (VIIb) in the presence of a reducing agent such as a sodium borohydride.



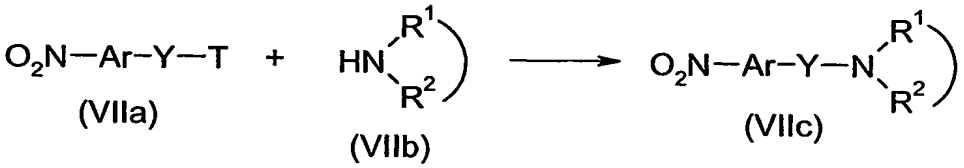
(VIII) (VIIb) (VIIc)

Compounds of formula (VIII) in which Y is a bond can be prepared by reaction of a compound of formula (IX) (in which Y is a bond) with an oxidant such as selenium dioxide in a solvent such as dioxane.



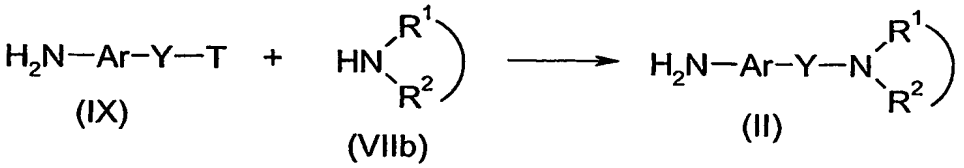
(IX) (VIII)

Compounds of formula VIIc can be prepared from a compound (VIIa) and an amine (VIIb) in which T is a leaving group.



(VIIa) (VIIb) (VIIc)

Compounds of formula (II) can be prepared from a compound (IX) and an amine (VIIb) in which T is a leaving group.



(IX) (VIIb) (II)

In the present invention, the compounds of formula (I) are believed to have a role in the treatment of depression, anxiety, obesity and/or diabetes. Compounds of the present invention are antagonists of a MCHR1 and can be used for the treatment of a disease caused by or attributable to a melanin-concentrating hormone. Compounds of the invention may reduce hunger, suppress appetite, control eating, and/or induce satiety.

The present invention provides methods for the treatment of several conditions or diseases such as obesity, diabetes, depression (eg., major depression and/or bipolar disorder), and/or anxiety. Such treatment comprises the step of administering a therapeutically effective amount of the compound of formula (I), including a salt, solvate, or physiologically functional derivative thereof to a mammal, preferably a human. Such treatment can also comprise the step of administering a therapeutically effective amount of a

pharmaceutical composition containing a compound of formula (I), including a salt, solvate, or physiologically functional derivative thereof to a mammal, preferably a human. As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and preventing or delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject.

As used herein, the term "therapeutically effective amount" means an amount of a compound of formula (I) which is sufficient, in the subject to which it is administered, to elicit the biological or medical response of a cell culture, tissue, system, animal (including human) that is being sought, for instance, by a researcher or clinician.

The precise therapeutically effective amount of the compounds of formula (I) will depend on a number of factors including, but not limited to, the age and weight of the subject being treated, the precise disorder requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. Typically, the compound of formula (I) will be given for treatment in the range of about 0.1 to about 200 mg/kg body weight of recipient (animal) per day and more usually in the range of about 1 to about 100 mg/kg body weight per day. In general, acceptable daily dosages, may be from about 0.1 to about 5000 mg/day, and preferably from about 0.1 to about 2000 mg/day. Unit doses will normally be administered once or more than once per day, preferably about 1 to about 4 times per day.

The administration of compounds of the invention to an animal, particularly a mammal such as a human, may be by way of oral (including sub-lingual), parenteral, nasal, rectal or transdermal administration. Preferably oral administration is employed.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of formula (I) may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation. Accordingly, the invention further provides a pharmaceutical composition comprising a compound of formula (I). The

pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s), and/or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I) with one or more pharmaceutically acceptable carriers, diluents, and /or excipients.

Pharmaceutical formulations may be presented in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of formula (I) or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example, by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the carrier(s), diluent(s), and/or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules (including soft gelatin capsules, hard gelatin capsules, and capsules made from other polymers such as hydroxypropylmethylcellulose) or tablets; powders or granules; solutions, emulsions, or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions. For instance, for oral administration in the form of a tablet or capsule (e.g., hard,

soft, elastic, gelatinous and/or non-gelatinous), the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, opaque, dispersing and coloring agent or dye can also be present.

Capsules are made by preparing a powder mixture as described above, and filling formed gelatin and/or non-gelatinous sheaths. Glidants and lubricants, such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, cellulosic polymers (e.g., hydrogels (HPMC, HPC, PVA), and the like), carboxymethylcellulose, polyethylene glycol, waxes, polyvinylpyrrolidone, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators (disintegrants) include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granuated by wetting with a

binder such as a syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material (e.g., HPMC) and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

The drug may be dissolved or dispersed in a volatile liquid such as water or ethanol and sprayed onto nonpareil beads. A binder such as sucrose, polyvinylpyrollidone, hydroxypropylmethylcellulose, or the like may be used. After at least one coating, protective coat(s) of a polymer such as hydroxypropylmethylcellulose may be applied and/or a sustained or delayed release coating(s) may be applied. Such coated beads may optionally be compressed into tablets or filled into capsules.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of active ingredient. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax, or the like. The compound of formula (I) can also

be incorporated into a candy, a wafer, and/or tongue tape formulation for administration as a "quick-dissolve" medicament. Oral dosage forms may be taken with or without water.

Additionally, the present invention comprises a compound of formula (I) in combination with at least one other species selected from the group consisting of at least one agent or drug for treating obesity, diabetes (e.g., rosiglitazone and/or metformin), hypertension, and arteriosclerosis. In particular, a compound of formula (I) may be combined with at least one species for the treatment of obesity selected from the group of human ciliary neurotrophic factor, a CB-1 antagonist or inverse agonist (such as rimonabant), a neurotransmitter reuptake inhibitor (such as sibutramine, bupropion, or bupropion HCl), a lipase inhibitor (such as orlistat), an MC4R agonist, a 5-HT2c agonist, and a ghrelin receptor agonist or antagonist.

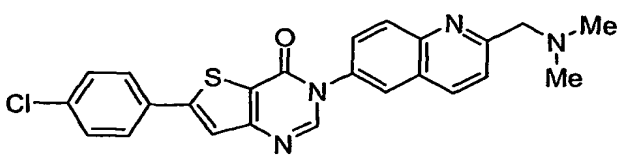
Also, the invention can be the use of a compound of formula (I) for the manufacture of a medicine (that is, medicament) for the treatment of a condition selected from the group consisting of obesity, diabetes, depression, and anxiety in a mammal.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way, the invention being defined by the claims which follow. All references cited in this specification are hereby incorporated by reference.

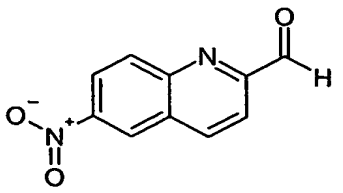
Reagents are commercially available or are prepared according to procedures in the literature.

Experimental Section

Example 1

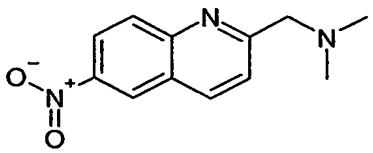


6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 6-nitroquinoline-2-carbaldehyde

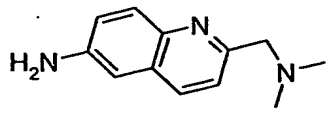
To a hot solution of selenium dioxide (41.6 g, 375 mmol) in dioxane (185 mL) and water (35 mL) was added 2-methyl-6-nitroquinoline (47.0 g, 250 mmol). The mixture was refluxed for 30 minutes. The selenium black was filtered off and the filtrate was concentrated by rotary evaporation. The resulting solid was filtered, washed with a saturated solution of sodium bicarbonate and then water, and dried to give the product as a tan solid (44.8 g, 89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.21 (d, J = 2.6 Hz, 1H), 8.97 (d, J = 8.5 Hz, 1H), 8.59 (dd, J = 2.6 Hz, J' = 9.2 Hz, 1H), 8.44 (d, J = 9.2 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H).



Step B: *N*,*N*-dimethyl-1-(6-nitroquinolin-2-yl)methanamine

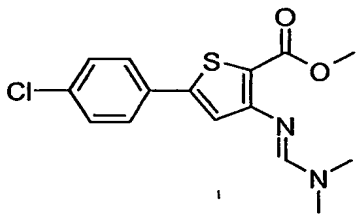
To a solution of 6-nitroquinoline-2-carbaldehyde (the intermediate produced in Example 1, Step A; 44.8 g, 221 mmol) in dichloroethane (800 mL) and methanol (320 mL) was added dimethylamine (221 mL, 442 mmol, 2 M in THF) and acetic acid (13.3 g, 221 mmol). The mixture was stirred at room temperarture for 20 min at which point sodium triacetoxyborohydride (65.6 g, 309 mmol) was added in 3 portions with vigorous mechanical stirring. The reaction mixture was stirred overnight. To the reaction mixture was added saturated sodium bicarbonate solution (300 mL) and the mixture was extracted with dichloromethane (2 x 400 mL). The organic layer was filtered through Celite. The filtrate was washed with brine (200 mL), dried and concentrated to give a tan solid (41.1 g, 80% yield). ^{1}H NMR (300 MHz,

DMSO-d_6) δ 9.05 (d, J = 2Hz), 8.67 (d, J = 9.6 Hz, 1H), 8.43 (dd, J = 2.2 Hz, J' = 12.3 Hz), 8.17 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H), 3.75 (s, 2H), 2.24 (2, 6H).



Step C: 2-[(dimethylamino)methyl]-6-quinolinamine

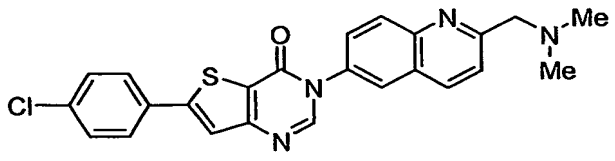
N,*N*-Dimethyl(6-nitro-2-quinolinyl)methanamine (the intermediate produced in Example 1, Step B; 365 mg, 1.58 mmol) was dissolved in EtOH. A catalytic amount of Pd/C was added. The mixture was degassed and was stirred under 1 atm H_2 for 5 h. The mix was filtered through celite and the solvents were removed to give the desired intermediate (290 mg, 91%). ^{1}H NMR ($CDCl_3$): δ 2.30 (6H, s), 3.68 (2H, s), 6.87 (1H, m), 7.11 (1, m), 7.15 (1H, s), 7.43 (1H, d, J = 8.8 Hz), 7.86 (1H, m). LCMS m/z = 202 (m + H^+).



Step D: methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate

A mixture of methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (37.3 mmol, 10.0 g) and N,N-dimethylformamide dimethyl acetal (74.7 mmol, 8.9 g) in ethanol (350 mL) was heated to reflux for 3 hours. The solvent was removed by rotary evaporation. To the residue 15 mL of toluene was added and the solvent was removed by rotary evaporation. This was repeated three times. To the resulting sticky residue, 20 mL hexanes were added followed by the gradual addition of ethyl acetate at 0°C until it solidified. The resulting solid was collected by filtration giving the desired intermediate (11.9 g, 98.9%). ^{1}H

NMR ($CDCl_3$): δ 3.08 (6H, d, J = 6.5 Hz), 3.81 (3H, s), 6.98 (1H, s), 7.35 (2H, d, J = 8.6 Hz), 7.53 (2H, d, J = 8.5 Hz), 7.69 (1H, s). LCMS m/z = 323 (m + H^+).

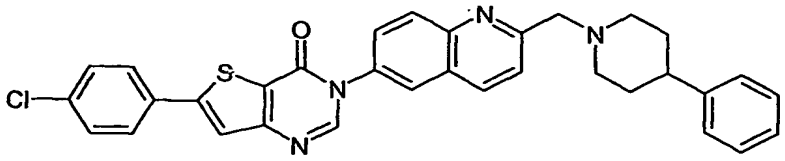


Step E: 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

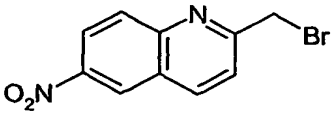
A 2 M solution of $AlMe_3$ in hexanes (0.96 mL, 1.92 mmol) was added slowly to a solution of 2-[(dimethylamino)methyl]quinolin-6-amine (the intermediate produced in Example 1, Step C; 0.34 g, 1.69 mmol) in dichloroethane (6 mL) at room temperature under N_2. After 15 min, a solution of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (the intermediate produced in Example 1, Step D; 0.50 g, 1.54 mmol) in dichloroethane (3 mL) was added and stirred at room temperature for 0.5 h. The solution was heated to reflux for 3 h then cooled to room temperature. Formic acid (6 mL) was added carefully and the mixture was heated to reflux for 4 h. Upon cooling to room temperature, an aqueous 1 N NaOH solution (50 mL) was added followed by CH_2Cl_2 (400 mL) and water (300 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound) as a tan solid (0.79 g) with ca. 85% purity. The solid was partially dissolved in hot $CHCl_3$ (20 mL), filtered, and concentrated. The resulting solid was dissolved in $CHCl_3$ (15 mL) and then Et_2O (25 mL) was added which produced a white precipitate. The solid was filtered and dried under vacuum to give 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound) as a white powder (0.33 g, 48%). The remaining impure material was subsequently purified in the same manner as described above to yield an additional 0.10 g of the title compound (63% overall yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 7.9 Hz, 1H), 8.25 (s, 1H), 8.21 (d, J = 8.2 Hz, 1H),

7.91 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 2.4, 9.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 3.83 (s, 2H), 2.37 (s, 6H). EI-LCMS *m/z* 447 (M+H).

Example 2

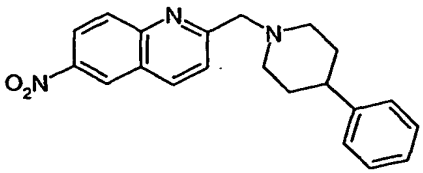


6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



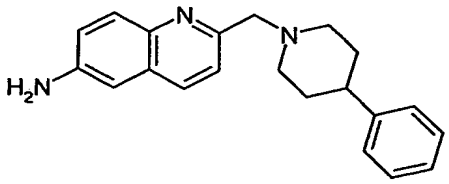
Step A: 2-(bromomethyl)-6-nitroquinoline

A solution of 2-methyl-6-nitroquinoline (3.0 g, 15.9 mmol) and N-bromosuccinimide (3.11 g, 17.49 mmol) in 36 mL chloroform in a pyrex round bottomed flask was stirred in the presence of a UV lamp at 40 °C for 2 d . After cooling, the mixture was washed with aqueous sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organic layers dried over sodium sulfate. Concentration followed by column chromatography on silica gel using hexane:ethyl acetate 7:3 afforded 2-(bromomethyl)-6-nitroquinoline as pale yellow solid (2.67 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.78 (d, J = 8.6 Hz, 1H), 8.52 (d, J = 9.8 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 4.93 (s, 2H); ES-LCMS *m/z* 267 (M+H).



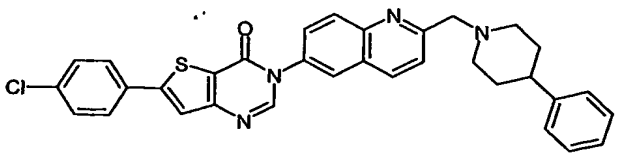
Step B: 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline

To a solution of 2-(bromomethyl)-6-nitroquinoline (the intermediate produced in Example 2, Step A; 1.0 g, 3.76 mmol) in THF at room tempreature was added Hunig's base (1.31 mL, 7.52 mmol) followed by the addition of 4-phenylpiperidine (0.61 g, 3.76 mmol). The contents were stirred for 3 h at room temperature. The crude reaction mixture was concentrated and loaded directly over a silica gel column using hexane:ethyl acetate 1:1 as the eluent to afford 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline as a brown solid (1.05 g, 81%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.67 (d, J = 9.0 Hz, 1H), 8.43 (d, J = 9.4 Hz, 1H), 8.16 (d, J = 9.4 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.29 – 7.14 (m, 5H), 3.83 (s, 2H), 2.94 (m, 2H), 2.51 (m, 2H), 2.23 (m, 2H), 1.73 – 1.67 (m, 3H); ES-LCMS *m/z* 348 (M+H).



Step C: 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine

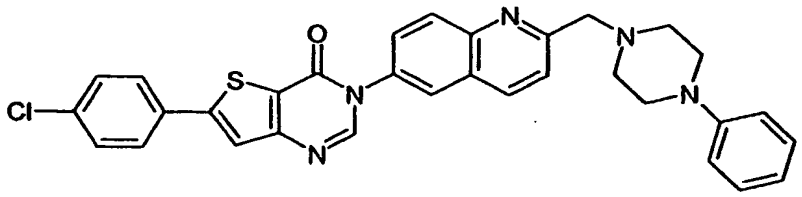
To a solution of 6-nitro-2-[(4-phenylpiperidin-1-yl)methyl]quinoline (the intermediate produced in Example 2, Step B; 1.0 g, 2.88 mmol) in 30 mL THF/EtOH (1:1) was added 0.1 g of Pd/C (10%) and the contents stirred under hydrogen gas (40 psi) for 6 h. The reaction was then filtered through celite, washed with EtOH and the contents concentrated under vacuum to afford 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine as a green solid (0.8g, 87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.39 – 7.10 (m, 6H), 6.78 (s, 1H), 3.45 (s, 2H), 2.94 (m, 2H), 2.52 (m, 2H), 2.16 (m, 2H), 1.74 – 1.65 (m, 3H); ES-LCMS *m/z* 320 (M+H).



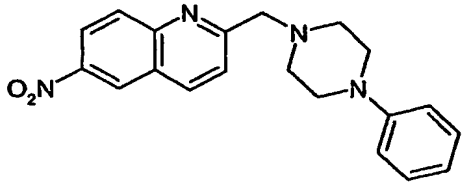
Step D: 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

To 2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-amine (the intermediate produced in Example 2, Step C; 0.160 g, 0.506 mmol) was added methyl 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (0.163 g, 0.506 mmol) and 0.5 g of phenol as the solvent. The reaction mixture was heated from 100 °C to 135 °C over a period of 1.5 h. The crude mixture was loaded over a silica gel column using DCM/MeOH (95:5) to afford 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one (the title compound) as a yellow solid (0.085 g, 30%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.59 (s,1H), 8.32 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.03 – 7.90 (m, 5H), 7.60 (d, J= 8.4 Hz, 1H), 7.35 – 7.21 (m, 6H), 4.76 (s, 2H), 3.61 – 3.49 (m, 2H), 3.28 – 3.15 (m, 2H), 2.87 (m, 1H), 2.22 – 1.96 (m, 4 H); ES-LCMS *m/z* 563 (M+H).

Example 3



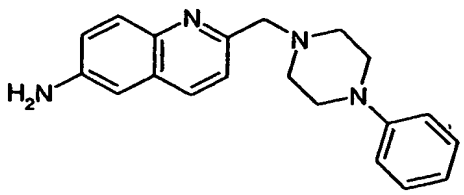
6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one



Step A: 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline

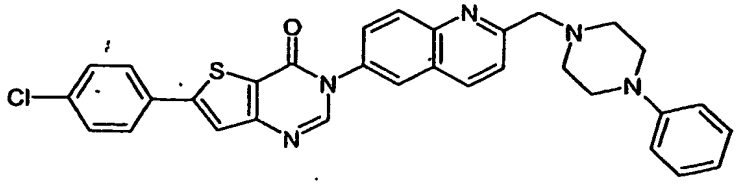
6-Nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-

(bromomethyl)-6-nitroquinoline with 1-phenylpiperazine. The compound was purified by column chromatography on silica gel, eluting with a gradient of 40% ethyl acetate in hexane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.69 (d, J = 8.6 Hz, 1H), 8.45 (d, J = 9.1 Hz, 1H), 8.18 (d, J = 9.1 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.20 (m, 2H), 6.92 (m, 2H), 6.77 (m, 1H) 3.87 (s, 2H), 2.61 (m, 4H), 2.48 (m, 4H); ES-LCMS *m/z* 349 (M+H).



Step B: 2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-amine

2-[(4-Phenylpiperazin-1-yl)methyl]quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline (Example 3, Step A) with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.92 (m, 2H), 6.79 (m, 2H), 5.53 (s, 2H), 3.69 (s, 2H), 3.14 (m, 4H), 2.58 (m, 4H); ES-LCMS *m/z* 319 (M+H).

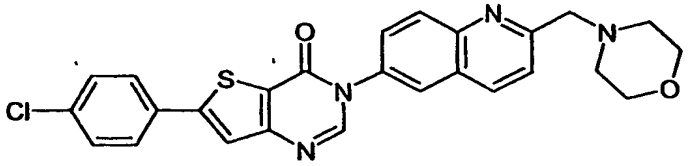


Step C: 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

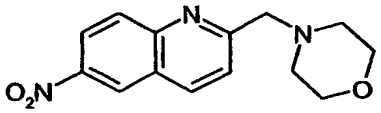
6-(4-Chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene]amino}thiophene-2-carboxylate (Example 1, Step

D) with 2-[(4-phenylpiperazin-1-yl)methyl]quinolin-6-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.60 (s,1H), 8.32 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 8.03 – 7.94 (m, 4H), 7.84 (d, J= 8.4 Hz, 1H), 7.60 (m, 2H), 7.28 (m, 1H), 7.16 (m, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 4.84 (s, 2H), 3.54 (m, 4H), 2.07 (m, 4H); ES-LCMS *m/z* 564 (M+H).

Example 4

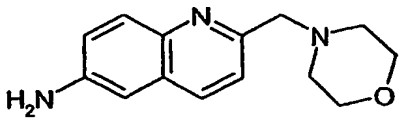


6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one



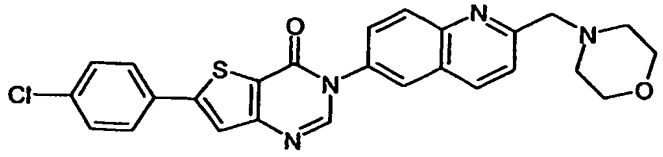
Step A: 2-(morpholin-4-ylmethyl)-6-nitroquinoline

2-(Morpholin-4-ylmethyl)-6-nitroquinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with morpholine. The desired compound was purified by column chromatography on silica gel, eluting with a gradient of 80% ethyl acetate in hexane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.72 (d, J = 8.6 Hz, 1H), 8.48 (d, J = 9.1 Hz, 1H), 8.21 (d, J = 9.2 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 3.89 (s, 2H), 3.66 (m, 4H), 2.54 (m, 4H); ES-LCMS *m/z* 274 (M+H).



Step B: 2-(morpholin-4-ylmethyl)quinolin-6-amine

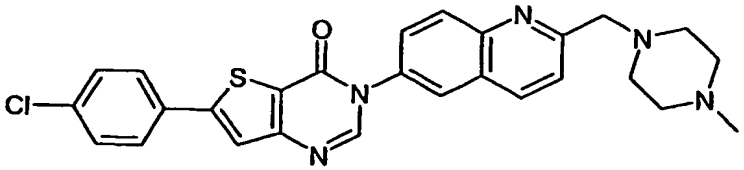
2-(Morpholin-4-ylmethyl)quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.21 – 7.11 (m, 1H), 6.81 (m, 1H), 5.55 (s, 2H), 3.65 (s, 2H), 3.61 (m, 4H), 2.51 (m, 4H); ES-LCMS *m/z* 244 (M+H).



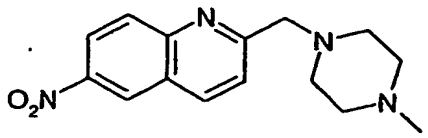
Step C: 6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-d]pyrimidin-4(3H)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-(morpholin-4-ylmethyl)quinolin-6-amine (Example 4, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 8.01 (s, 1H), 7.95 – 7.90 (m, 3H), 7.75 (d, J = 8.4 Hz, 1H), 7.59 (m, 2H), 3.79 (s, 2H), 3.61 (m, 4H), 2.48 (m, 4H); ES-LCMS *m/z* 509 (M+H).

Example 5

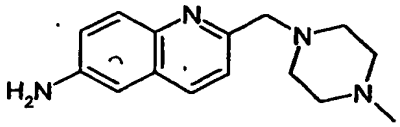


6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one



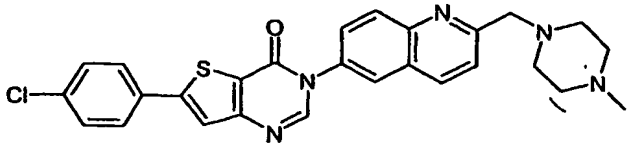
Step A: 2-[(4-methylpiperazin-1-yl)methyl]-6-nitroquinoline

2-[(4-Methylpiperazin-1-yl)methyl]-6-nitroquinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with 1-methylpiperazine. The desired compound was purified by column chromatography on silica gel, eluting with 100% ethyl acetate. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.73 (d, J = 8.5 Hz, 1H), 8.49 (d, J = 9.3 Hz, 1H), 8.21 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 3.89 (s, 2H), 2.75 (m, 4H), 2.54 (m, 4H), 2.45 (s, 3H); ES-LCMS *m/z* 287 (M+H).



Step B: 2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-amine

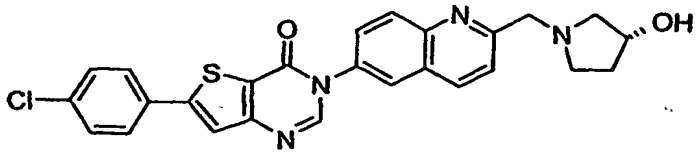
2-[(4-Methylpiperazin-1-yl)methyl]quinolin-6-amine was prepared using a similar experimental procedure as in Example 1, Step C by reducing 6-nitro-2-[(4-phenylpiperazin-1-yl)methyl]quinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.95 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.81 (s, 1H), 5.57 (s, 2H), 3.71 (s, 2H), 2.76 (m, 4H), 2.53 (m, 4H), 2.43 (s, 3H); ES-LCMS *m/z* 257 (M+H).



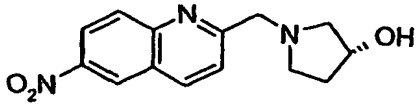
Step C: 6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-yl}thieno[3,2-d]pyrimidin-4(3H)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-[(4-methylpiperazin-1-yl)methyl]quinolin-6-amine (Example 5, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 8.02 (s, 1H), 7.94 – 7.88 (m, 3H), 7.75 (d, J = 8.5 Hz, 1H), 7.59 (m, 2H), 3.82 (s, 2H), 2.64 – 2.37 (m, 11H); ES-LCMS *m/z* 502 (M+H).

Example 6

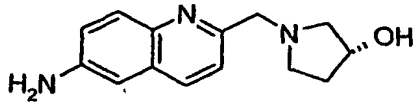


6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: (3*R*)-1[(6-nitro-2quinolinyl)methyl]-3-pyrrolidinol

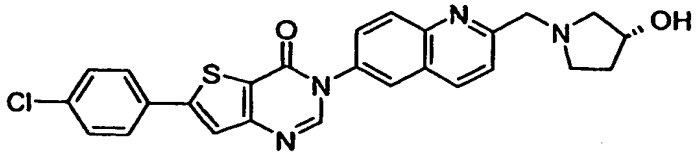
This intermediate was prepared from (3*R*)-hydroxypyrrolidine and 6-nitroquinoline-2-carbaldehyde using the techniques described in Example 1, Step B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H); 8.69 (d, J = 9.6 Hz, 1H); 8.30 (d, J = 8.4 Hz, 1H); 8.17 (d, J = 9.2 Hz, 1H); 7.75 (d, J = 8.4 Hz, 1H); 4.41-4.39 (m, 1H); 4.04 (s, 2H); 3.04-2.98 (m, 1H); 2.82-2.73 (m, 1H); 2.55-2.49 (m, 1H); 2.28-2.20 (m, 1H); 1.86-1.79 (m, 1H). ES-LCMS *m/z* 296 (M+Na).



Step B: (3*R*)-1-[(6-amino-2-quinolinyl)methyl]-3-pyrrolidinol

This intermediate was prepared from the intermediate produced in Example 6,

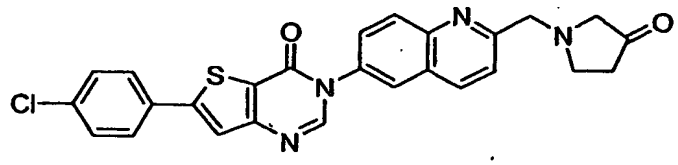
Step A, by using the techniques described in Example 1, Step C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 1H); 7.79 (d, J = 9.2 Hz, 1H); 7.49 (d, J = 8.8 Hz, 1H); 7.29 (d, J = 9.2 Hz, 1H); 6.97 (s, 1H); 4.62 (s, 2H); 4.41(m, 1H); 3.48-3.39 (m, 2H); 3.26-3.14 (m, 2H); 2.19-2.02 (m, 1H); 1.95-1.85 (m, 1H). ES-LCMS *m/z* 244 (M+H).



Step C: 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was obtained from the intermediate produced from Example 6, Step B, by using the techniques described in Example 2, Step D. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.17 (m, 3H); 7.89 (s, 1H); 7.74 (d, J = 8.4 Hz, 1H); 7.67-7.65 (m, 3H); 7.56 (s, 1H), 7.40 (d, J = 7.6 Hz, 2H); 4.40 (bs, 1H); 4.05 (s, 2H); 3.30-2.99 (m, 1H); 2.85-2.70 (m, 2H); 2.54-2.50 (m, 1H); 2.32-2.20 (m, 1H); 1.91-1.75 (m, 1H). ES-LCMS *m/z* 489 (M+H).

Example 7

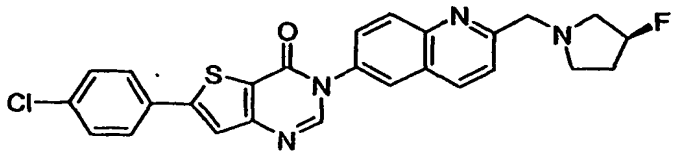


6-(4-chlorophenyl)-3-{2-[(3-oxo-1-pyrrolidinyl)methyl]-6-quinolinyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

To oxalyl chloride (2 M solution in dichlomethane, 5.5 mL, 11 mmol) at -60 °C, was added DMSO (1.7 mL, 22 mmol), The resulting mixture was stirred at this temperature for 5 minutes. In a separate flask, 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (33 mg, 0.67 mmol) was dissolved in 2mL dichloromethane. The above prepared oxidant solution (1.5 mL, 0.67 mmol) was added at –60 °C. After the mixture

was stirred for 15 minutes. 0.5 mL triethylamine was added. Then the mixture was let warmed up to room temperature. The reaction was quenched by pouring the reaction mixture into saturated sodium bicarbonate solution. It was then partitioned between dichloromethane and aqueous layers and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried and the solvents were removed by evaporation *in vacuo*. The residue was purified by flash chromatography eluting with 3% methanol in dichloromethane. The title compound was obtained (26 mg) as light tan solid. ^{1}H NMR (400 MHz, CDCL3) δ 8.27-8.22 (m, 3H); 7.92(s, 1H); 7.77 (d, J = 8.8 Hz, 1H); 7.69-7.66 (m, 3H); 7.57 (s, 1H); 7.46 (d, J = 8.4 Hz, 2H); 4.11(s, 2H); 3.11 (s, 2H); 3.09 (t, J = 7.2 Hz, 2H); 2.49 (t, J = 7.4 Hz, 2H). ES-LCMS *m/z* 487 (M+H).

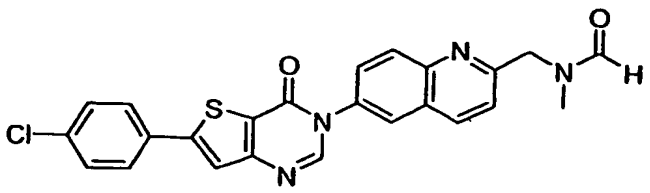
Example 8



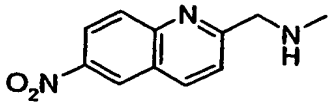
6-(4-chlorophenyl)-3-(2-{[(3*S*)-3-fluoropyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

To 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidinyl]methyl}-6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (the title compound from Example 6, 20 mg, 0.04 mmol) in dichloroethane (1.5 mL), diethylaminosulfur trifluoride (DAST, 10 mg, 0.06 mmol) was added at -30 °C. The mixture was stirred overnight and allowed to warm to room temperature. The mixture was poured into an ice cold saturated sodium bicarbonate solution and extracted with dichlomethane. After the combined organic layers were washed and dried, the solvent was removed *in vacuo*. The residue was purified by flash chromatography eluting with 5% methanol in dichlomethane affording the title compound as solid (12 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.19 (m, 3H); 7.89(s, 1H); 7.76-7.72 (m, 2H); 7.67 (d, J = 8.4 Hz, 2H); 7.56 (s, 1H); 7.45 (d, J = 8.4 Hz, 2H); 5.30-5.13 (m, 1H); 4.05(s, 2H); 3.03-2.82 (m, 2H); 2.60 (m, 1H); 2.28-2.04 (m, 2H). ES-LCMS *m/z* 490 (M+H).

Example 9

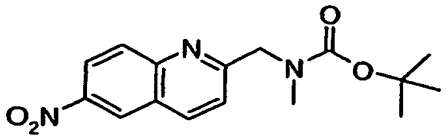


[6-(6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl)-2-quinolinyl]methyl(methyl)formamide



Step A: *N*-methyl(6-nitro-2-quinolinyl)methanamine

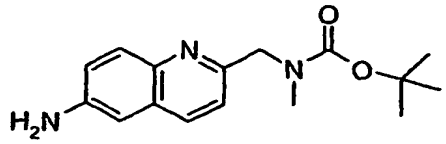
This intermediate was prepared from methylamine and 6-nitroquinoline-2-carbaldehyde using the techniques described in Example 1, Step B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H); 8.64 (d, J = 8,8 Hz, 1H); 8.42 (d, J = 8.8 Hz, 1H); 8.13 (d, J = 9.2 Hz, 1H); 7.79 (d, J = 8.4 Hz, 1H); 3.98 (s, 2H); 2.32(s, 3H). ES-LCMS *m/z* 218 (M+H).



Step B: *tert*-butyl methyl[(6-nitro-2-quinolinyl)methyl]carbamate (two rotamers)

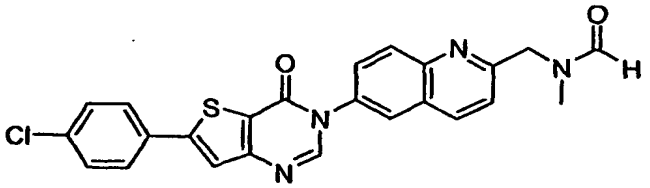
The intermediate obtained in Example 9, Step A (1.4 g, 6.45 mmol) was dissolved in dichloromethane. Triethylamine (0.91 g, 9.03 mmol) and di-*tert*-butyl dicarbonate (1.97 g, 9.03 mmol) were added. The reaction was stirred for 10 minutes and diluted with dichloromethane, washed sequentially with saturated solutions of sodium bicarbonate and sodium chloride, dried, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using a 2:1 hexane:ethyl acetate mixture as the eluent

to provide 1.95 g (95% yield) of the desired intermediate as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (bs, 1H); 8.46 (d, J = 9.2 Hz, 1H); 8.31 (bs, 1H); 8.14 (d, J = 8.8 Hz, 1H); 7.54-7.48 (m, 1H); 4.76 (s) and 4.72(s), total 2H; 3.00(s) and 2.93 (s), total 3H; 1.51 (s) and 1.39 (s), total 9H. ES-LCMS *m/z* 318 (M+H).



Step C: *tert*-butyl (6-amino-2-quinolinyl)methyl(methyl)carbamate

This intermediate was prepared by starting with the intermediate produced in Example 9, Step B, and subjecting it to the conditions found in Example 1, Step C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 8.8 Hz, 1H); 8.14 (bs, 1H); 7.55-7.49 (m, 2H); 7.14 (bs, 1H); 4,81 (s, 2H); 2.96(bs, 3H); 1.40(s) and 1.18(s), total 9H. ES-LCMS *m/z* 288 (M+H).

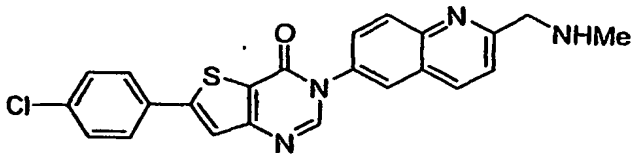


Step D: [6-(6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl)-2-quinolinyl]methyl(methyl)formamide (rotamers)

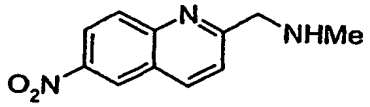
The intermediate obtained in Example 9, Step C (430 mg, 1.5 mmol) was dissolved in 1,2-dichlorethane under a nitrogen atmosphere. A 2 M solution of trimethylaluminum in toluene (1.1 mL, 2.2 mmol) was added dropwise via syringe. The mixture was stirred 20 minutes at room temperature. Methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]-amino}thiophene-2-carboxylate (the intermediate from Example 1, Step D; 483 mg,1.5 mmol) was added and the mixture was heated at reflux overnight. The solvent was removed under reduced pressure and the resultant residue was dissolved in formic acid and heated at reflux for 2 hours. The formic acid was removed

under reduced pressure and the resultant residue was dissolved in dichlormethane, washed with a saturated solution of potassium carbonate, dried, and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using a 2-3% MeOH-dichloromethane mixture as the eluent to provide the title compound (150 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.19 (m, 3H); 7.92 (d, J = 8.8 Hz, 1H); 7.78 (d, J = 8.8 Hz, 1H); 7.67 (d, J = 8.4 Hz, 2H); 7.57 (s, 1H); 7.50-7.40 (m, 3H); 4.87(s) and 4.74(s), total 2H;); 3.02 (s) and 2.90 (s), total 3H. ES-LCMS *m/z* 461 (M+H).

Example 10

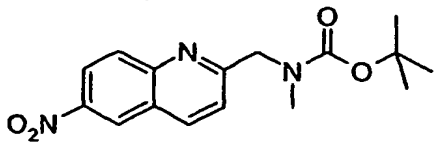


6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



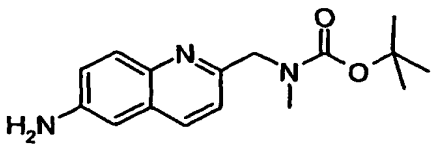
Step A: 1-(6-nitroquinolin-2-yl)methanamine

Methylamine (7.3 mL of a 2.0 M solution in tetrahydrofuran) was added to a solution of 2-(bromomethyl)-6-nitroquinoline (0.86 g, 3.23 mmol) in 10 mL of tetrahydrofuran. The mixture was stirred at room temperature for 1.5 hours. The solvent was evaporated and the crude product was purified by chromatography on silica gel. Elution with a gradient of 0-10% methanol in dichloromethane gave 0.47 g (67%) of desired product as a brown gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.1 (s, 1H), 8.71 (d, J=8.5 Hz, 1H), 8.48 (d, J=9.2 Hz, 1H), 8.18 (d, J=9.2 Hz, 1H), 7.80 (d, J=8.5 Hz, 1H), 4.23 (s, 2H), 3.34 (br s, 1H) 2.50 (s, 3H). ES-LCMS m/z 218 (M+H).



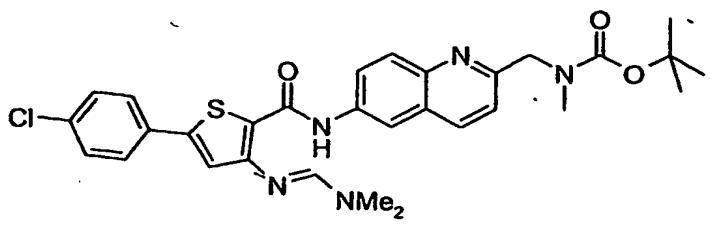
Step B: *tert*-butyl methyl[(6-nitroquinolin-2-yl)methyl]carbamate

Di(*tert*-butyl) dicarbonate (0.71 g, 3.24 mmol) and triethylamine (0.30mL, 2.16 mmol) were added to a partial solution of *N*-methyl-1-(6-nitroquinolin-2-yl)methanamine (0.47 g, 2.16 mmol) in 20 mL of dichloromethane. The resulting homogeneous solution was stirred at room temperature for 30 minutes. The solvent was evaporated and the residue purified by chromatography on silica gel with a gradient of 0-50% ethyl acetate in hexane to give 0.295 g (43%) of desired product as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.70 (d, J=8.6 Hz, 1H), 8.46 (d, J=9.1 Hz, 1H), 8.15 (d, J=9.3 Hz, 1H), 7.56 (m, 1H), 4.70 (s, 2H), 2.96 (m, 3H), 1.46 and 1.24 (s, 9H).



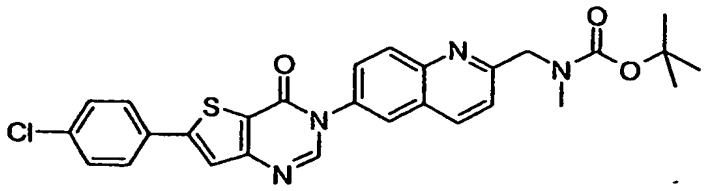
Step C: *tert*-Butyl (6-aminoquinolin-2-yl)methyl(methyl)carbamate

Palladium (5% by weight on activated carbon, 0.098 g, 0.046 mmol) was added to a solution of *tert*-butyl methyl[(6-nitroquinolin-2-yl)methyl]carbamate (0.292 g, 0.92 mmol) in 20 mL of ethyl acetate in a Fisher-Porter tube. The mixture was evacuated and flushed with nitrogen, then evacuated and filled with 50 psi of hydrogen. After 1 hour, the reaction mixture was filtered through Celite and the solvent evaporated to give 0.254 g (96%) of desired product as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J=8.4 Hz, 1H), 7.61 (d, J=9.0 Hz, 1H), 7.11 (d, J=9.0 Hz, 1H), 7.10 (d, J=8.4 Hz, 1H), 6.76 (s, 1H), 5.52 (s, 2H), 4.48 (s, 2H), 2.82 (s, 3H), 1.43 and 1.31 (s, 9H).



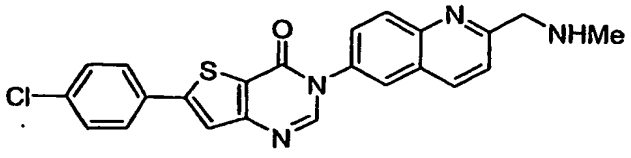
Step D: *tert*-Butyl (6-{[(5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thien-2-yl)carbonyl]amino}quinolin-2-yl)methyl(methyl)carbamate

A solution of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]-amino}thiophene-2-carboxylate (the intermediate from Example 1, Step D; 0.067 g, 0.209 mmol) and *tert*-butyl (6-aminoquinolin-2-yl)methyl(methyl)carbamate (0.050 g, 0.174 mmol) in 2 mL of anhydrous tetrahydrofuran was cooled to 0 °C. Sodium hexamethyldisilazane (0.26 mL of a 1.0 M solution in tetrahydrofuran) was added dropwise over 5 minutes. The mixture was stirred at 0°C for 10 minutes and then allowed to warm to room temperature. After 2 hours, saturated aqueous ammonium chloride (0.5 mL) was added and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. Chromatography on silica gel with a gradient of 0-100% ethyl acetate in hexane gave 0.029 g (24%) of desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.49 (s, 1H), 8.43 (d, J=2.4 Hz, 1H), 8.3 (d, J=9.0 Hz, 1H), 7.95 (d, J=9.0 Hz, 1H), 7.87 (s, 1H), 7.80 (d, J=2.4 Hz, 1H), 7.76 (1/2 Abq, J=8.6 Hz, 2H), 7.55 (1/2 Abq, J=8.6 Hz, 2H), 7.32 (m, 1H), 4.61 (s, 2H), 3.24 and 3.22 (s, 6 H), 2.90 (m, 3H), 1.46 and 1.31 (s, 9H). APCI-LCMS m/z 578 (M+H).



Step E: *tert*-butyl {6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]quinolin-2-yl}methyl(methyl)carbamate

A catalytic amount of p-toluenesulfonic acid was added to a suspension of *tert*-butyl (6-{[(5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}thien-2-yl)carbonyl]amino}quinolin-2-yl)methyl(methyl)carbamate (0.025 g, 0.043 mmol) in 5 mL of absolute ethanol. A homogeneous solution was obtained upon heating to reflux. After 2 hours, the mixture was cooled to room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane:methanol. Macroporous triethylammonium methylpolystyrene carbonate (0.050 mg, 0.14 mmol) was added, and the mixture was stirred at room temperature for 18 hours. The resin was filtered off and the solution was concentrated to give the desired product as a white solid (0.023 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.44 (d, J=8.6 Hz, 1H), 8.20 (s, 1H), 8.08 (d, J=8.6 Hz, 1H), 8.01 (s, 1H), 7.94 (1/2 Abq, J=8.6 Hz, 2H), 7.90 (d, J=8.6 Hz, 1H), 7.58 (1/2 Abq, J=8.6 Hz, 2H), 7.45 (m, 1H), 4.67 (s, 2H), 2.92 (m, 3H), 1.45 and 1.28 (s, 9H). APCI-LCMS m/z 533 (M+H).

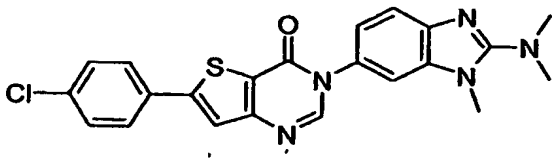


Step F: 6-(4-chlorophenyl)-3-{2-[(methylamino)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

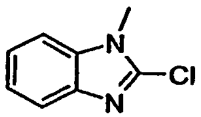
Trifluoroacetic acid (0.050 mL) was added to a solution of *tert*-butyl {6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]quinolin-2-

yl}methyl(methyl)carbamate (0.023 g, 0.043 mmol) in dichloromethane (2 mL). The mixture was stirred at room temperature for 20 hours. The solvent was evaporated and 0.5 mL of methanol, followed by 10 mL of diethyl ether was added. The mixture was filtered and the collected white solid was dried under vacuum to give 0.018 g (77%) of the title compound as its trifluoroacetic acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (br s, 2H), 8.61 (s, 1H), 8.55 (d, J=8.5 Hz, 1H), 8.31 (s, 1H), 8.20 (d, J=9.1 Hz, 1H), 8.04 (s, 1H), 8.03 (d, J=9.1 Hz, 1H), 7.96 (1/2 Abq, J=8.6 Hz, 2H), 7.69 (d, J=8.5 Hz, 1H), 7.61 (1/2 Abq, J=8.6 Hz, 2H), 4.61 (s, 2H), 2.76 (s, 3H). ES-LCMS m/z 433 (M+H).

Example 11

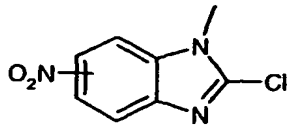


6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 2-chloro-1-methyl-1*H*-benzimidazole

Dimethylsulfate (11 mL) was added drop-wise (via addition funnel) to a solution of 2-chlorobenzimidazole (10 g, 63.06 mmol) and 10 N NaOH (aq) (15 mL) in H_2O (115 mL) at 0°C. The mixture was then allowed to warm to room temperature, and was then stirred at room temperature for 2 h. TLC data (50% EtOAc/Hexanes) indicated that 2-chlorobenzimidazole was consumed. A tan precipitate had formed. The precipitate was filtered through a buchner funnel, the filter cake washed with H_2O, and the resulting precipitate was air-dried to afford a tan solid, 2-chloro-1-methyl-1*H*-benzimidazole (9.41 g, 90% yield). ^{1}H NMR (DMSO-*d*6) δ 7.56 (t, 2H, J=14.5Hz), 7.26 (m, 2H), 3.76 (s, 1H). ES-LCMS *m/z* 167 (100), (M+H).



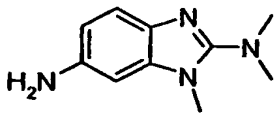
Step B: mixture of 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole and 2-chloro-1-methyl-6-nitro-1*H*-benzimidazole

Conc. H_2SO_4 (20 mL) was added drop-wise (via addition funnel) to a mixture of the intermediate produced in Example 11, Step A (9.41 g, 56.48 mmol) and conc. HNO_3 at 0 °C. The mixture stirred at 0 °C for 2h. TLC data (50% EtOAc/Hexanes) indicated that starting material was consumed. The reaction mixture was poured into ice water (500 mL), and the resulting yellow precipitate was filtered through a buchner funnel, the filter cake washed with H_2O, and the resulting precipitate was air-dried to afford a yellow solid, a mixture of 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole, and 2-chloro-1-methyl-6-nitro-1*H*-benzimidazole (8.78 g, 73% yield). ^{1}H NMR (DMSO-*d*6) δ 8.65 (s, 1H,), 8.47 (s, 1H), 8.21 (d, 1H, J=11.2Hz), 8.12 (d, 1H, J=11.2Hz), 7.82 (d, 1H, J=9.0Hz), 7.77 (d, 1H, J=9Hz), 3.89 (s, 1H), 3.85 (s, 1H). ES-LCMS *m/z* 212 (100), (M+H).

Step C: 2-chloro-1-methyl-1*H*-benzimidazol-6-amine and 2-chloro-1-methyl-1*H*-benzimidazol-5-amine

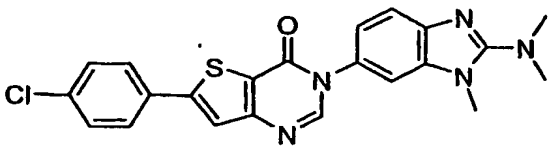
The intermediate produced in Example 11, Step B (7.78 g, 36.77 mmol) was added portion-wise to a solution of $Sn(II)Cl_2 \cdot 2H_2O$ (24.89 g, 110.30 mmol) in conc. HCl (100 mL) at room temperature. The mixture was stirred at room temperature for 15 min, and then at 100 °C for 1 h. TLC data (30% CH_3CN/CH_2Cl_2) indicated that starting material was consumed. The reaction mixture was cooled to room temperature, made pH=8 with 10 N NaOH (aq), charged with Rochelle's salt (100 mL), then extracted with EtOAc (4 x 200 mL). The organics were dried over $MgSO_4$ (anhy.), filtered, and concentrated

to dryness. The resulting crude was chromatographed on a SiO_2 column (0-30% CH_3CN/CH_2Cl_2 over 30 min, then 30% CH_3CN/CH_2Cl_2 for 60 min) to afford a pink solid 2-chloro-1-methyl-1*H*-benzimidazol-5-amine (1.82 g, 27% yield), (Rf=0.18 in 30% CH_3CN/CH_2Cl_2), ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.7 (s, 3 H) 4.9 (s, 2 H) 6.6 (dd, *J*=8.6, 1.9 Hz, 1 H) 6.7 (d, *J*=1.7 Hz, 1 H) 7.2 (d, *J*=8.6 Hz, 1 H), ES-LCMS *m/z* 182 (60), (M+H); and a pink solid, 2-chloro-1-methyl-1*H*-benzimidazol-6-amine (2.5 g, 52% yield), (Rf=0.33 in 30% CH_3CN/CH_2Cl_2), ^{1}H NMR (DMSO-*d*6) δ 7.20 (d, 1H), 6.53 (m, 2H), 5.09 (s, 2H), 3.60 (s, 3H), ES-LCMS *m/z* 182 (100), (M+H).



Step D: N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine

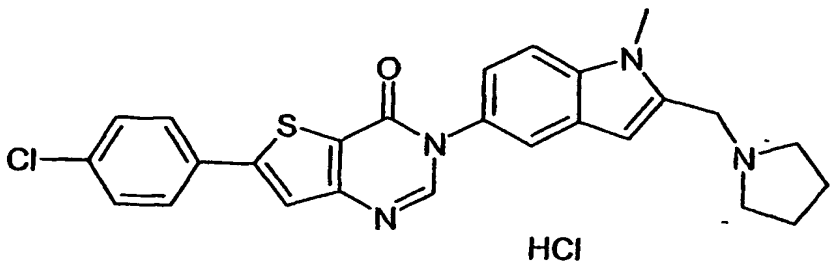
2-Chloro-1-methyl-1*H*-benzimidazol-6-amine (Example 11, Step C; 1 g, 5.51 mmol) and 2 M dimethylamine in MeOH (30 mL) was stirred at 160 °C in a sealed tube for 17.5 h. TLC data (10% $MeOH/CH_2Cl_2$) indicated that starting material was consumed. The reaction mixture was cooled to room temperature, then concentrated to dryness. The resulting crude was chromatographed on a SiO_2 column (0-6% $MeOH/CH_2Cl_2$ over 30 min, then 6% $MeOH/CH_2Cl_2$ for 30 min). Fractions corresponding to product (Rf=0.34 in 10% $MeOH/CH_2Cl_2$) were concentrated to dryness to afford a pink solid, N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine (640 mg, 61% yield). ^{1}H NMR (DMSO-*d*6) δ 7.01 (d, 1H, J=8.3Hz), 6.42 (s, 1H), 6.36 (d, 1H, J=10.3), 4.77 (s, 2H), 3.44 (s, 3H), 2.78 (s, 6H). ES-LCMS *m/z* 191 (100), (M+H).



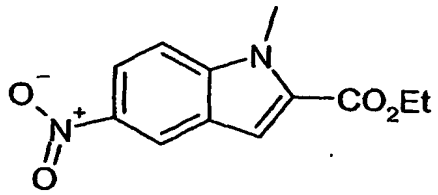
Step E: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The intermediate from Example 11, Step D (1.09 g, 3.36 mmol) and Example 1, Step D (640 mg, 3.36 mmol) was mixed in phenol (5 g) and stirred from room temperature to 150 °C over ~30 min, then at 150 °C for 1 h. LC-MS data indicated that some starting marterial remained. Additional intermediate produced in Example 1, Step D (300 mg, 0.93 mmol) was added and the mixture stirred at 150 °C for 1h. LC-MS data indicated that the intermediate produced in Example 11, Step D was consumed. The reaction mixture was cooled to ~60°C, then poured into MeOH (100 mL). The resulting precipitate was filtered, washed with MeOH, and air-dried to afford the title compound as a tan solid (1.37 g, 93% yield). ^{1}H NMR (DMSO-*d*6) δ 8.45 (s, 1H), 8.00 (s, 1H), 7.95 (d, 2H, J=8.5Hz), 7.58 (m, 3H), 7.47 (d, 1H, J=8.3Hz) 7.19 (d, 1H, J=10.3), 3.65 (s, 3H), 2.98 (s, 6H). ES-LCMS *m/z* 436 (100), (M+H).

Example 12



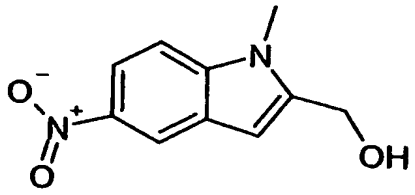
6-(4-chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1H-indol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride



Step A: ethyl 1-methyl-5-nitro-1H-indole-2-carboxylate

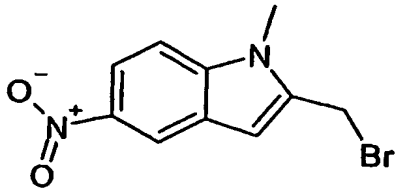
Ethyl 5-nitro-1H-indole-2-carboxylate (1.75 g, 7.46 mmol) was dissolved in DMF (30 mL) and sodium hydride (0.6 g of a 60% dispersion) was added. The

reaction was stirred at room temperature for 30 min. Methyl iodide (1.324g, 9.33 mmol) was added. The reaction was stirred overnight at room temperature. The reaction was diluted with water (100 mL) and the precipitate was collected by suction filtration. The precipitate was taken up in EtOAc (100 mL) and washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated to afford 1.175 g (4.74 mmol, 63%) of the product as a red brown solid. ^1H NMR ($CDCl_3$) δ 8.65 (d, 1H, J = 2 Hz), 8.25 (dd, 1H, J = 2.2 Hz, 11.3 Hz), 7.45 (s, 1H), 7.43 (d, 1H, J = 11.3 Hz), 4.40 (q, 2H, J = 7.1 Hz), 4.13 (s, 3H), 1.42 (t, 3H, J = 7.2 Hz).



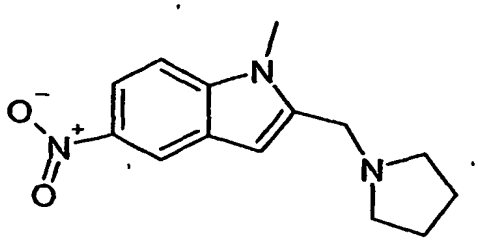
Step B: (1-methyl-5-nitro-1H-indol-2-yl)methanol

Ethyl 1-methyl-5-nitro-1H-indole-2-carboxylate (1.175 g, 4.74 mmol) was dissolved in THF (50 mL). Alane (11 mL of a 1M sol) was added. The reaction was heated to 70 °C and stirred for 6h and then cooled to room temperature, quenched with methanol (50 mL), diluted with water (100 mL), and extracted with EtOAc (2 x 100 mL). The combined organics were washed with water (3 x 150 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.664g (3.22 mmol, 90%) of the product as a red brown solid. ^1H NMR ($CDCl_3$) δ 8.54 (d, 1H, J = 2 Hz), 8.14 (dd, 1H, J = 2.2 Hz, 9.1 Hz), 7.35 (d, 1H, J = 9.2 Hz), 6.62 (s, 1H), 4.82 (s, 2H), 3.90 (s, 3H).



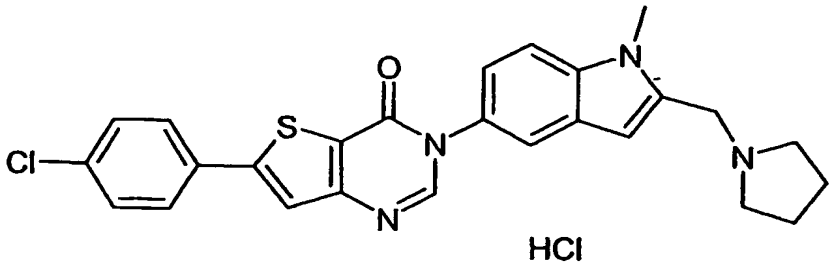
Step C: 2-(bromomethyl)-1-methyl-5-nitro-1H-indole

(1-Methyl-5-nitro-1H-indol-2-yl)methanol (0.664 g, 3.223 mmol) was dissolved in CH_2Cl_2 (50 mL). Carbon tetrabromide (1.336 g, 4.03 mmol) was added. The mix was cooled to 0 °C and then triphenylphosphine (1.268 g, 4.83 mmol) in small portions over 1 h. The reaction was stirred overnight, washed with water (1 x 100 mL), and the organics dried over $MgSO_4$, filtered, and concentrated. The mix was filtered on a chromatatron plate to remove baseline impurities. The resultant solid was taken up in minimal CH_2Cl_2 and triturated with hexane to give 0.238 g (0.853 mmol, 26%) of the desired product as a yellow solid. ^1H NMR ($CDCl_3$) δ 8.55 (d, 1H, J = 2.2 Hz), 8.16 (dd, 1H, J = 2.2 Hz, 9.1 Hz), 7.35 (d, 1H, J = 9.1 Hz), 6.76 (s, 1H), 4.65 (s, 2H), 3.92 (s, 3H).



Step D: 1-methyl-5-nitro-2-(pyrrolidin-1-ylmethyl)-1H-indole

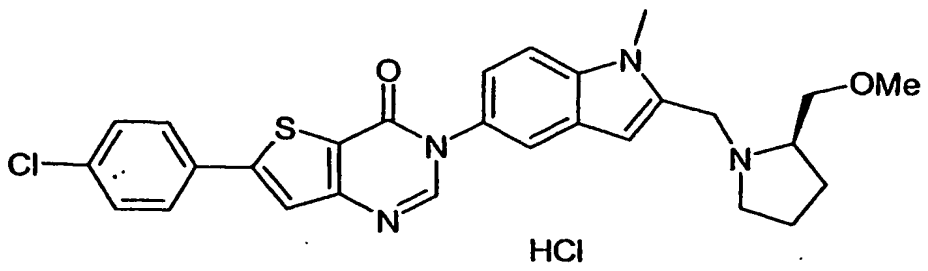
2-(Bromomethyl)-1-methyl-5-nitro-1H-indole (0.134 g, 0.50 mmol) was taken up in DMF (5 mL). Pyrrolidine (0.060 mL, 0.75 mmol) was added along with triethylamine (0.134 mL, 1 mmol). The reaction was heated to 80 °C and stirred for 2 h and then cooled to room temperature and partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was removed and the organics were washed with water (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated to give 0.112 g (0.432 mmol, 87%) of the product as a yellow semisolid. ^1H NMR ($CDCl_3$) δ 8.50 (d, 1H, J = 2.2 Hz), 8.09 (dd, 1H, J = 2.2 Hz, 9.1 Hz), 7.30 (d, 1H, J = 9.1 Hz), 6.53 (s, 1H), 3.85 (s, 3H), 3.78 (s, 2H), 2.5 (bs, 4H), 1.8 (bs, 4H).



Step E: 6-(4-chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1H-indol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride

1-Methyl-5-nitro-2-(pyrrolidin-1-ylmethyl)-1H-indole (0.112 g, 0.43 mmol) was taken up in EtOAc (10 mL) and hydrogenated over 10% Pd/C on a Parr hydrogenator under 50 psi of H_2. After 2h, the mixture was filtered through celite and concentrated. The residue was taken up in a minimal amount of CH_2Cl_2 and methyl 5-(4-chlorophenyl)-3-{[(dimethylamino)methylene]amino}thiophene-2-carboxylate (the intermediate from Example 1, Step D; 0.115 g, 0.43 mmol) and phenol (0.5 g) were added. The mix was heated to 130 °C and stirred for 30 min, cooled to room temperature and purified on a chromatatron (100% CH_2Cl_2 to 80:20 CH_2Cl_2:MeOH). The product was treated with 1 N HCl in Et_2O, stirred for 2h, and concentrated to give 0.071 g (0.139 mmol, 33%) of the title compound as a cream colored solid. ^{1}H NMR (DMSO-d_6) δ 10.2 (bs, 1H), 8.5 (s, 1H), 8.05 (s, 1H), 7.92 (d, 2H, J = 7.5 Hz), 7.77 (s, 1H), 7.67 (d, 1H, J = 8.8 Hz), 7.58 (d, 2H, J = 8.5 Hz), 7.34 (dd, 1H, J = 2.1 Hz, 8.1 Hz), 6.85 (s, 1H), 4.68 (d, 2H, J = 5.5 Hz), 3.2 (bs, 2H, 2.05 (bs, 2H), 1.95 (bs, 2H). LRMS M+ H 475.

Example 13

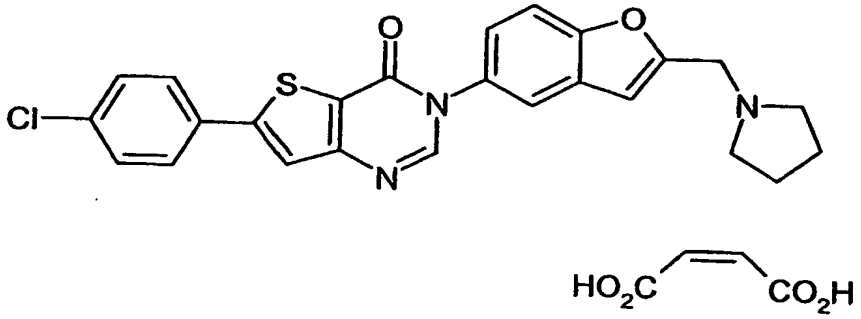


6-(4-chlorophenyl)-3-(2-{[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-

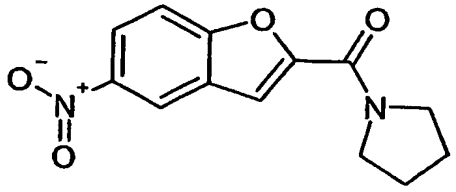
1-methyl-1H-indol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride

The title compound was synthesized using the same procedures as that for 6-(4-chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1H-indol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride (Example 12), using (2*R*)-2-(methoxymethyl)pyrrolidine instead of pyrrolidine. ^{1}H NMR ($CDCl_3$) δ 12.9 (bs, 1H), 8.6 (s, 1H), 7.80 (s, 1H, 7.68 (d, 2H, J = 8.5 Hz), 7.65 (s, 1H), 7.55 (d, 1H, J = 8.8 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.30 (d, 1H, J = 8.9 Hz), 6.80 (s, 1H), 4.94 (d, 1H, J = 14,3 Hz), 4.46 (m, 2H), 4.03 (s, 3H), 3.74-3.60 (m, 2H), 3.55 (s, 3H), 3.00 (bs, 2H), 2.28 (bs, 1H), 2.17 (bs, 1H), 1.96 (bs, 2H) LRMS M+ H 519.

Example 14



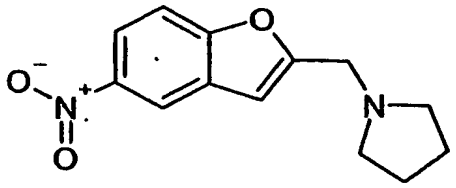
6-(4-Methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt



Step A: 1-[(5-Nitro-1-benzofuran-2-yl)carbonyl]pyrrolidine

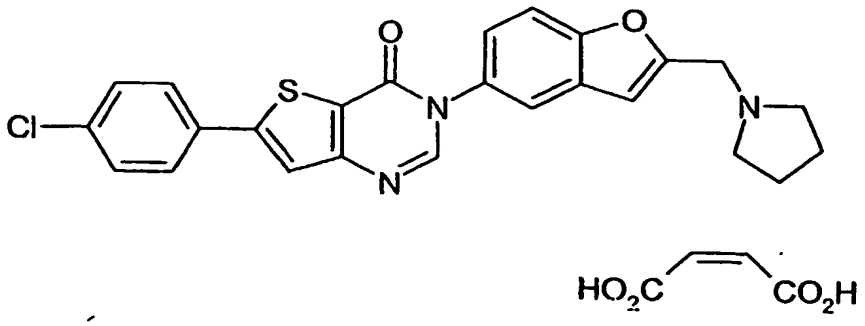
5-Nitro-1-benzofuran-2-carboxylic acid (0.50 g, 2.41 mmol) was suspended in thionyl chloride (5 mL) and heated to reflux. The reaction was stirred for 16 h and then concentrated to dryness. The residue was taken up in DMF (5 mL) and pyrrolidine (0.343 g, 4.82 mmol) and triethylamine (0.488 g, 4.82 mmol)

were added. The mixture was heated to 80 °C and stirred for 2 h. The reaction mixture was then cooled to room temperature and water (50 mL) was added. The resultant solid was collected and taken up in EtOAc (50 mL). The organics were washed with water (3 x 150 mL), dried over $MgSO_4$, filtered and concentrated to give 0.454 g (1.75 mmol, 72%) of the title compound as a light yellow solid. ^1H NMR ($CDCl_3$) δ 8.61 (dd, 1H, J = 2.2 Hz), 8.32 (dd, 1H, J = 2.2 Hz, 9.0 Hz), 7.63 (d, 1H, J = 9.0 Hz), 7.51 (s, 1H), 3.94 (t, 2H, J = 6.8 Hz), 3.71 (t, 2H, J = 7.0 Hz), 2.06 (p 2H, J = 6.7 Hz), 1.97 (p, 2H, J = 7.0 Hz).



Step B: 1-[(5-Nitro-1-benzofuran-2-yl)methyl]pyrrolidine

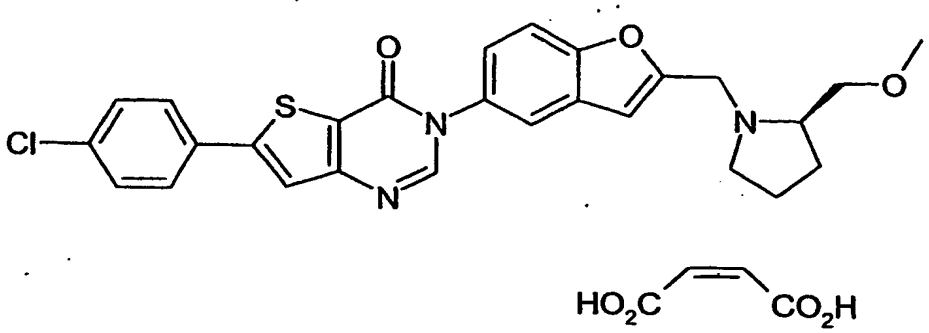
1-[(5-Nitro-1-benzofuran-2-yl)carbonyl]pyrrolidine (the intermediate from Step A; 0.363 g, 1.40 mmol) was suspended in dry THF (5 mL). Alane (4 mL of a 1 M soln) was added and the mixture was heated to 70 °C and stirred for 2 h. The mix was then cooled to room temperature and quenched with methanol (10 mL). The mixture was diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organics were washed with water (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated to give 0.210 g (0.854 mmol, 61%) of the product as a dark golden oil. ^1H NMR ($CDCl_3$) δ 8.45 (d, 1H, J =2.2 Hz), 8.19 (dd, 1H, J = 2.2 Hz, 8.8 Hz), 7.53 (d, 1H, J = 9 Hz), 6.74 (s, 1H), 3.85 (s, 2H), 2.65 (bs, 4H), 1.85 (bs, 4H).



Step C: 6-(4-Methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt

1-[(5-Nitro-1-benzofuran-2-yl)methyl]pyrrolidine (the intermediate from Step B; 0.210 g, 0.85 mmol) was taken up in EtOAc (20 mL) and hydrogenated over 10% Pd/C using H_2 (1 atm). The reaction was filtered through celite and concentrated. The resultant residue was taken up in minimal amount of CH_2Cl_2. Phenol (0.5 g) and methyl 5-(4-chlorophenyl)-3-{[(dimethylamino)methylene]-amino}thiophene-2-carboxylate (the intermediate from Example 1, Step D; 0.275 g, 0.85 mmol) were added. The mix was heated to 130 °C and stirred for 1h and then cooled to room temperature and purified on a chromatatron (100% CH_2Cl_2 to 95:5 CH_2Cl_2:MeOH). The isolated product was taken up in CH_2Cl_2 (5 mL) and 1 eq of maelic acid was added. The mixture was stirred overnight and the precipitate was collected to give 0.089 g (0.154 mmol, 18%) of the title compound as a white solid. ^1H NMR (DMSO-d_6) δ 10.3 (bs, 1H), 8.5 (s, 1H), 7.99 (s, 1H), 7.92 (m, 3H), 7.80 (d, 1H, J = 8.8 Hz), 7.55 (m, 3H), 7.2 (s, 1H), 6.0 (s, 2H), 4.8 (bs, 2H), 3.4 (bs 4H), 1.9 (bs, 4H). LRMS M+ H 461

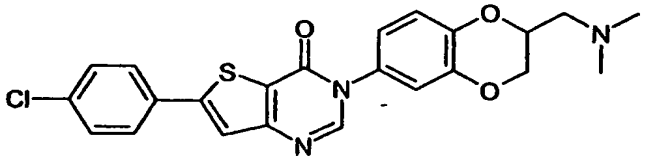
Example 15



3-(2-{[(2*R*)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-1-benzofuran-5-yl)-6-(4-methylphenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt

The title compound was synthesized using the same procedures as that for 6-(4-Methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt (Example 14) using (2*R*)-2-(methoxymethyl)-pyrrolidine instead of pyrrolidine. ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 1H), 7.80-7.75 (m, 3H), 7.6 (s, 1H), 7.5-7.4 (m, 3H), 7.10 (s, 1H) 6.4 (bs, 3H), 4.85-4.6 (bm, 2H), 4.0-3.8 (bs, 2H), 3.8-3.7 (bs, 2H), 3.4 (s 3H), 3,25 (bs, 1H), 2.2 9bs, 2H), 1.9 (bs, 2H). LRMS M+ H 507.

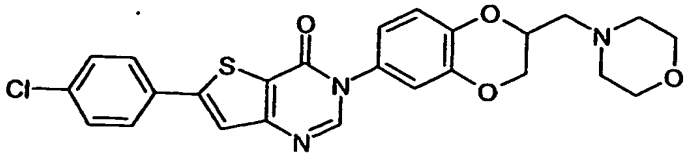
Example 16



6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

To 2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-amine (produced according to patent application WO0121577, 0.100 g, 0.481 mmol) were added methyl 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D; 0.155 g, 0.481 mmol) and 0.150 g of phenol as the solvent. The reaction mixture was heated at 135 °C for 2 h. The crude mixture was loaded over a silica gel column using DCM/MeOH (100:5) to afford 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one (the title compound) as a solid (0.096 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.98 (s, 1H), 7.93 (d, J=8.6 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 7.15 (d, J=1.8 Hz, 1H), 7.03 (m, 2H), 4.40 (m, 2H), 4.04 (dd, J=11.5 and 7.0 Hz, 1H), 2.56 (br, 2H), 2.27 (s, 6H); ES-LCMS *m/z* 454 (M+H).

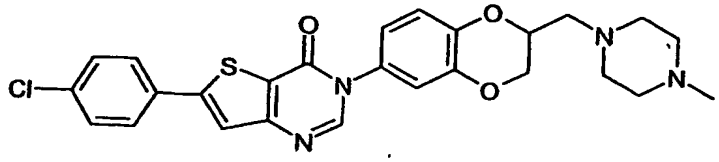
Example 17



6-(4-chlorophenyl)-3-[2-(4-morpholinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting morpholine for dimethylamine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.97 (s, 1H), 7.93 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.14 (d, J=2.2 Hz, 1H), 7.02 (m, 2H), 4.46 (m, 1H), 4.38 (dd, J=11.5 and 2.2 Hz, 1H), 4.06 (dd, J=11.5 and 7.1 Hz, 1H), 3.59 (t, J=14.6 Hz, 4H), 2.61 (m, 2H), 2.50 (br, 4H); ES-LCMS *m/z* 496 (M+H).

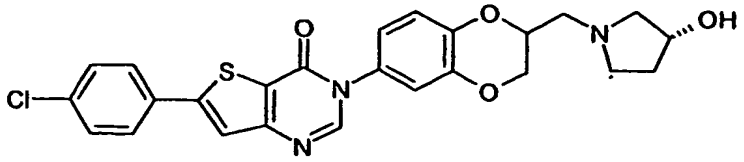
Example 18



6-(4-chlorophenyl)-3-{2-[(4-methyl-1-piperazinyl)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting 4-methyl-piperazine for dimethylamine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.97 (s, 1H), 7.93 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.13 (d, J=2.2 Hz, 1H), 7.02 (m, 2H), 4.42 (m, 1H), 4.36 (dd J=11.5 and 2.2 Hz, 1H), 4.04 (dd J=11.5 and 7.2 Hz, 1H), 2.60 (d, J=6.9 Hz, 2H), 2.50 (br, 4H), 2.33 (br, 4H), 2.16 (s, 3H); ES-LCMS *m/z* 509 (M+H).

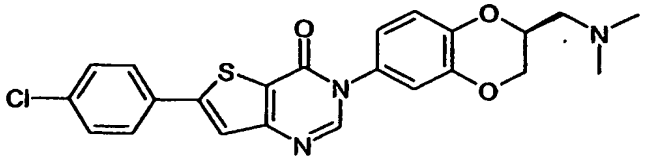
Example 19



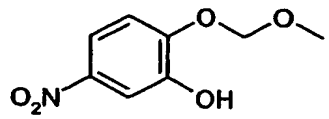
6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}-2,3-dihydro-1,4-benzodioxin-6-yl)thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting (3*R*)-3-hydroxy-pyrrolidine for dimethylamine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.97 (s, 1H), 7.93 (d, d=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 7.13 (d, J=2.0 Hz, 1H), 7.02 (m, 2H), 4.70 (br, 1H), 4.38 (m, 2H), 4.19 (m, 1H), 4.07 (m, 1H), 2.38-3.32 (m, 6H), 1.98 (m, 1H), 1.55 (m, 1H); ES-LCMS *m/z* 496 (M+H).

Example 20



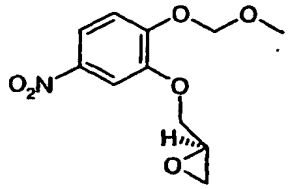
6-(4-chlorophenyl)-3-{(2*S*)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one



Step A: 2-{[(methyloxy)methyl]oxy}-5-nitrophenol

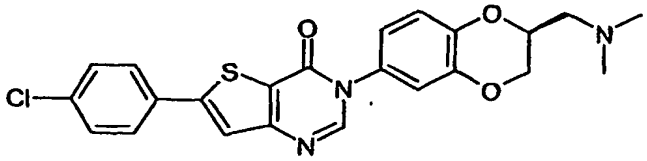
To a solution of 4-nitrocatechol (12.7 g, 81.9 mmol) in 100mL of dry DMF were added potassium carbonate (13.5 g, 97.8 mmol) and chloromethyl methyl ether (6.2 mL, 97.8 mmol) at 40 °C. The mixture was stirred at that temperature for an hour and then solvent was removed. Water was added and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine and dried over magnesium sulfate. Concentration followed by column chromatography on silica gel using

a 4:1 mixture of hexane:ethyl acetate afforded 2-{[(methyloxy)methyl]oxy}-5-nitrophenol as a solid (9.4 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.18 (d, J=8.8 Hz, 1H), 5.98 (s, 1H), 5.32 (s, 2H), 3.53 (s, 3H).



Step B: (2*R*)-2-{[(2-{[(methyloxy)methyl]oxy}-5-nitrophenyl)oxy]methyl}oxirane

To a solution of 2-{[(methyloxy)methyl]oxy}-5-nitrophenol (1g, 5mmol), triphenylphosphine (3.95 g, 15 mmol) and (R)-glycidol (558 mg, 7.5 mmol) in 50 mL of dry DCM was added di-*tert*-butyl azodicarboxylate (3.47 g, 15 mmol) at room temperature. The reaction was stirred at room temperature overnight. Concentration followed by column chromatography on silica gel using a 4:1 hexane:ethyl acetate as the eluent afforded (2*R*)-2-{[(2-{[(methyloxy)methyl]oxy}-5-nitrophenyl)oxy]methyl}oxirane as a solid (0.75 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J=9.0 and 2.5 Hz, 1H), 7.82 (d, J=2.5 Hz, 1H), 7.22 (d, J=9.0, 1H), 5.31 (s, 2H), 4.42 (dd, J=11.3 and 2.6 Hz, 1H), 4.02 (dd, J=11.3 and 6.0 Hz, 1H), 3.52 (s, 3H), 3.42 (m, 1H), 2.94 (m, 1H), 2.79 (m, 1H); ES-LCMS *m/z* 278 (M+Na).

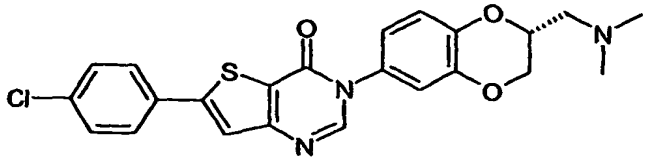


Step C: 6-(4-chlorophenyl)-3-{(2*S*)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

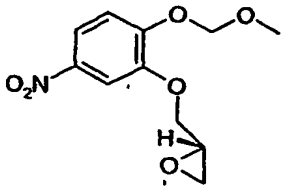
The title compound was synthesized by substituting (2*S*)-2-[(dimethylamino) methyl]-2,3-dihydro-1,4-benzodioxin-6-amine (the intermediate produced from (2*R*)-2-{[(2-{[(methyloxy)methyl]oxy}-5-nitrophenyl)oxy]methyl}oxirane (Example 20, Step B) according to patent application WO0121577) for 2-

[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-amine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.97 (s, 1H), 7.93 (d, J=8.5 Hz, 2H), 7.59 (d, J=8.5 Hz, 2H), 7.14 (d, J=2.0 Hz, 1H), 7.02 (m, 2H), 4.38 (m, 2H), 4.03 (dd, J=11.4 and 7.0 Hz, 1H), 2.54 (d, J=6.0 Hz, 2H), 2.25 (s, 6H); ES-LCMS *m/z* 454 (M+H).

Example 21

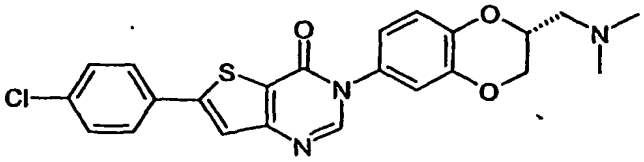


6-(4-chlorophenyl)-3-{(2*R*)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one



Step A: (2*S*)-2-{[(2-{[(methyloxy)methyl]oxy}-5-nitrophenyl)oxy]methyl}oxirane

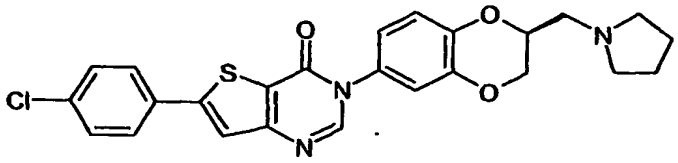
This intermediate was synthesized by substituting (*S*)-glycidol for (*R*)-glycidol and employing the techniques found in Example 20, Step B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J=9.0 and 2.6 Hz, 1H), 7.82 (d, J=2.6 Hz, 1H), 7.22 (d, J=9.0 Hz, 1H), 5.31 (s, 2H), 4.42 (dd, J=11.4 and 2.7 Hz, 1H), 4.03 (dd, J=11.4 and 6.0 Hz, 1H), 3.52 (s, 3H), 3.41 (m, 1H), 2.93 (m, 1H), 2.79 (m, 1H); ES-LCMS *m/z* 278 (M+Na).



Step B: 6-(4-chlorophenyl)-3-{(2*R*)-2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting (2R)-2-[(dimethylamino) methyl]-2,3-dihydro-1,4-benzodioxin-6-amine (the intermediate produced from (2*S*)-2-{[(2-{[(methyloxy)methyl]oxy}-5-nitrophenyl)oxy]methyl}oxirane (Example 21, Step A) according to patent application WO0121577) for 2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-amine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.97 (s, 1H), 7.93 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 7.14 (d, J=2.0 Hz, 1H), 7.02 (m, 2H), 4.38 (m, 2H), 4.03 (dd, J=11.4 and 7.0 Hz, 1H), 2.54 (d, J=6.2 Hz, 2H), 2.25 (s, 6H); ES-LCMS *m/z* 454 (M+H).

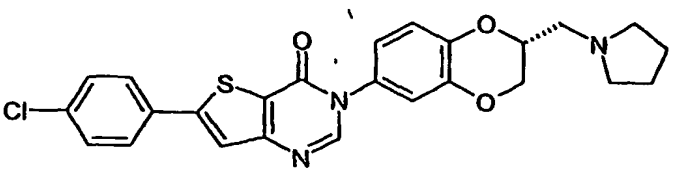
Example 22



6-(4-chlorophenyl)-3-[(2*S*)-2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting pyrrolidine for dimethylamine and employing the techniques found in Example 20. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.97 (s, 1H), 7.93 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 7.14 (d, J=2.0 Hz, 1H), 7.01 (2H), 4.38 (m, 2H), 4.05 (dd, J=11.7 and 7.3 Hz, 1H), 2.75 (m, 2H), 2.67 (m, 4H), 1.70 (s, 4H); ES-LCMS *m/z* 480 (M+H).

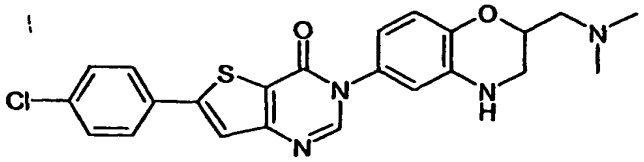
Example 23



6-(4-chlorophenyl)-3-[(2*R*)-2-(1-pyrrolidinylmethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting pyrrolidine for dimethylamine and employing the techniques found in Example 21. ^{1}H NMR (400 MHz, DMSO-d_6) δ) 8.37 (s, 1H), 7.97 (s, 1H), 7.93 (d, J=8.5 Hz, 2H), 7.59 (d, J=8.5 Hz, 2H), 7.14 (d, J=2.2 Hz, 1H), 7.01 (2H), 4.38 (m, 2H), 4.05 (dd, J=11.8 and 7.4 Hz, 1H), 2.73 (m, 2H), 2.57 (m, 4H), 1.70 (s, 4H); ES-LCMS *m/z* 480 (M+H).

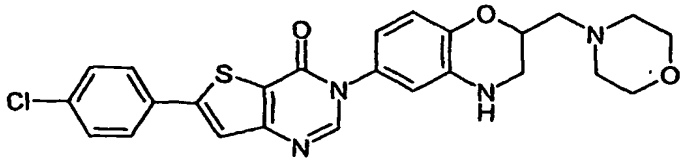
Example 24



6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting 2-[(dimethylamino)methyl]-3,4-dihydro-2*H*-1,4-benzoxazin-6-amine(the intermediate produced according to patent application WO0121577) for 2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-amine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.96 (s, 1H), 7.93 (d, J=8.6 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.4 Hz, 1H), 6.68 (d, J=2.5 Hz, 1H), 6.58 (dd, J=8.4 and 2.5 Hz, 1H), 6.14 (s, 1H), 4.19 (m, 1H), 3.38 (m, 1H), 3.05 (m, 1H), 2.50 (br, 2H), 2.25 (s, 6H); ES-LCMS *m/z* 453 (M+H).

Example 25

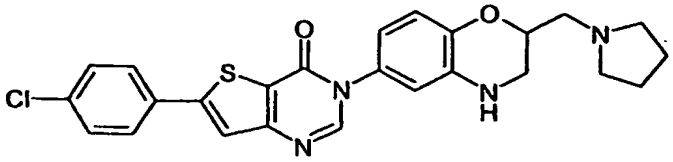


6-(4-chlorophenyl)-3-[2-(4-morpholinylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting morpholine for

dimethylamine and employing the techniques found in Example 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.92 (s, 1H), 7.89 (d, J=8.6 Hz, 2H), 7.55 (d, J=8.6 Hz, 2H), 6.76 (d, J=8.4 Hz, 1H), 6.64 (d, J=2.5 Hz, 1H), 6.54 (dd, J=8.4 and 2.5 Hz, 1H), 6.10 (s, 1H), 4.21 (m, 1H), 3.56 (t, J=4.6 Hz, 4H), 3.38 (m, 1H), 3.05 (m, 1H), 2.39-2.53 (m, 6H); ES-LCMS *m/z* 495 (M+H).

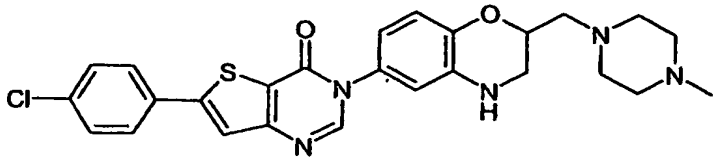
Example 26



6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting pyrrolidine for dimethylamine and employing the techniques found in Example 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.92 (s, 1H), 7.89 (d, J=8.6 Hz, 2H), 7.55 (d, J=8.6 Hz, 2H), 6.76 (d, J=8.4 Hz, 1H), 6.64 (d, J=2.5 Hz, 1H), 6.55 (d, J=8.4 and 2.5 Hz, 1H), 6.09 (s, 1H), 4.15 (m, 1H), 3.36 (m, 1H), 3.04 (m, 1H), 2.46-2.67 (m, 6H), 1.67 (br, 4H); ES-LCMS *m/z* 479 (M+H).

Example 27

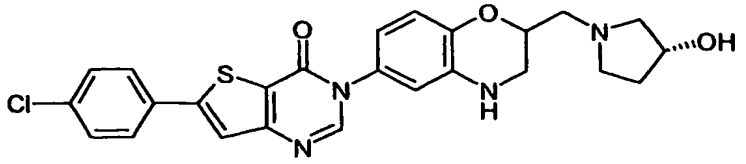


6-(4-chlorophenyl)-3-{2-[(4-methyl-1-piperazinyl)methyl]-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting 4-methyl-piperazine for dimethylamine and employing the techniques found in Example 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.95 (s, 1H), 7.92 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 6.78 (d, J=8.4 Hz, 1H), 6.67 (d, 2.4 Hz, 1H), 6.57 (dd, J=8.4 and 2.4 Hz, 1H), 6.12 (s, 1H), 4.21 (m, 1H), 3.39 (m, 1H), 3.06 (m, 1H), 2.20-

2.58 (m, 10H), 2.16 (s, 3H); ES-LCMS *m/z* 508 (M+H).

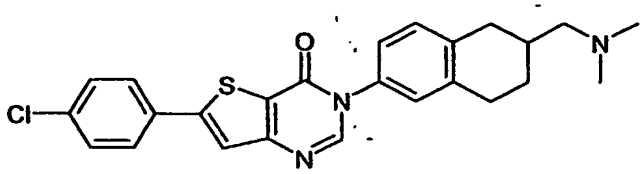
Example 28



6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl)thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting (3*R*)-3-hydroxy-pyrrolidine for dimethylamine and employing the techniques found in Example 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s; 1H), 7.95 (s, 1H), 7.92 (d, J=8.6 Hz, 2H), 7.58 (d, J=8.6 Hz, 2H), 6.79 (d, J=8.4 Hz, 1H), 6.67 (d, J=2.5 Hz, 1H), 6.57 (dd, J=8.4 and 2.5 Hz, 1H), 6.12 (s, 1H), 4.70 (m, 1H), 4.17 (m, 1H), 3.38 (m, 1H), 3.08 (m, 1H), 2.36-2.84 (m, 6H), 1.98 (m, 1H), 1.54 (m, 1H); ES-LCMS *m/z* 495 (M+H).

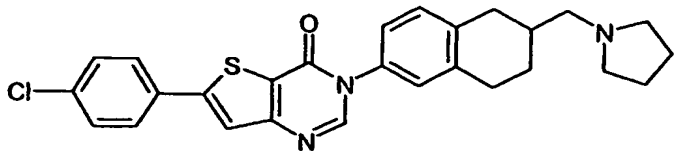
Example 29



6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl}thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting 6-[(dimethylamino) methyl]-5,6,7,8-tetrahydro-2-naphthalenamine (the intermediate produced according to patent application WO0121577) for 2-[(dimethylamino)methyl]-2,3-dihydro-1,4-benzodioxin-6-amine and employing the techniques found in Example 16. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.98 (s, 1H), 7.93 (d, J=8.6 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 7.24 (m, 3H), 2.95 (m, 1H), 2.82 (m, 2H), 2.43 (m, 2H), 2.2 (br, 6H), 1.96 (m, 2H), 1.36 (m, 2H); ES-LCMS *m/z* 450 (M+H).

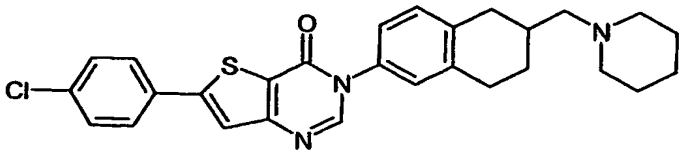
Example 30



6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting pyrrolidine for dimethylamine and employing the techniques found in Example 29. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.98 (s, 1H), 7.93 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.4 Hz, 2H), 7.26 (m, 3H), 2.99 (m, 1H), 2.83 (m, 2H), 2.46 (m, 7H), 1.98 (m, 2H), 1.72 (m, 4H), 1.39 (m, 1H); ES-LCMS *m/z* 476 (M+H).

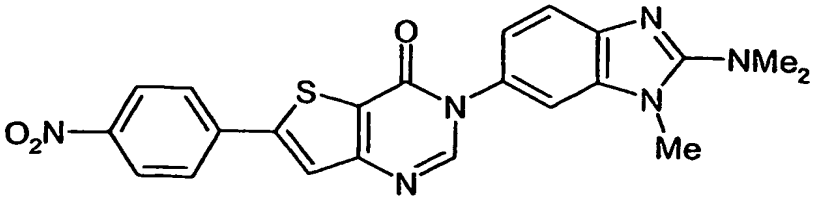
Example 31



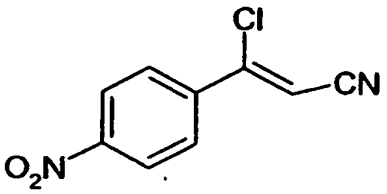
6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4 (3*H*)-one

The title compound was synthesized by substituting piperidine for dimethylamine and employing the techniques found in Example 29. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.98 (s, 1H), 7.94 (d, J=8.6 Hz, 2H), 7.59 (d, J=8.6 Hz, 2H), 7.25 (m, 3H), 2.91 (m, 1H), 2.82 (m, 2H), 2.34 (m, 4H), 2.23 (d, J=7.1 Hz, 2H), 1.97 (m, 2H), 1.53 (m, 4H), 1.40 (m, 4H); ES-LCMS *m/z* 490 (M+H).

Example 32

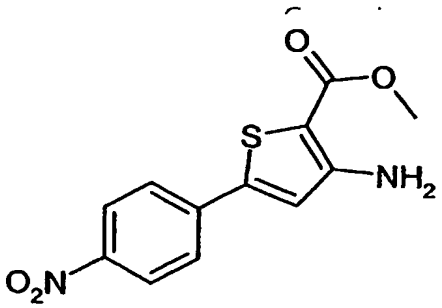


3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]-6-(4-nitrophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: (2Z)-3-chloro-3-(4-nitrophenyl)acrylonitrile

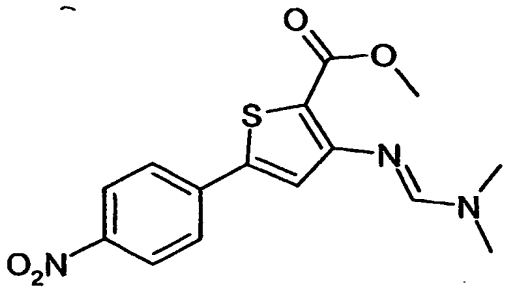
(2Z)-3-Chloro-3-(4-nitrophenyl)acrylonitrile was prepared as described in J. Prakt. Chem. *325*, 915 (1983) starting with 1-(4-nitrophenyl)ethanone. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.3 (d, J= 9.2 Hz, 2H), 7.9 (d, J= 9.2 Hz, 2H), 6.2 (s, 1H).



Step B: Methyl 3-amino-5-(4-nitrophenyl)thiophene-2-carboxylate

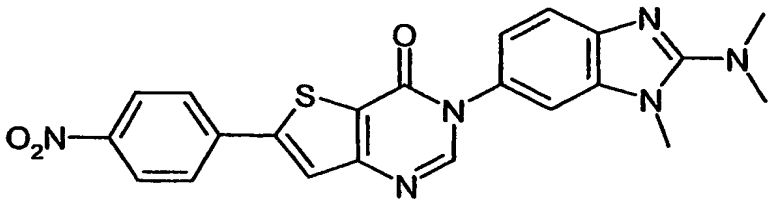
Methyl thioglycolate (0.517 g, 4.87 mmol) was added to a solution of sodium methoxide (0.26 g, 4.87 mmol) in 10 mL of methanol at room temperature. 3-Chloro-3-(4-nitrophenyl)acrylonitrile, from Step A above, (1.01 g, 4.87 mmol) was added and the resulting solution was heated at reflux for 10 minutes. The mixture was cooled to room temperature and filtered. The solid product

was washed with water and dried under vacuum to give 0.846 g (62 % yield) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J= 8.8 Hz, 2H), 7.91 (d, J= 8.8 Hz, 2H), 7.18 (s, 1H), 6.67 (br s, 2H), 3.76 (s, 3H). ES-LCMS m/z= 278 (M^+).



Step C: methyl 3-{[(1*E*)-(dimethylamino)methylene]amino}-5-(4-nitrophenyl)thiophene-2-carboxylate

This compound was prepared from methyl 3-amino-5-(4-nitrophenyl)thiophene-2-carboxylate from step B above as described in Example 1, Step D to give the desired intermediate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.2 (d, J= 8.8 Hz, 2H), 8.0 (d, J= 8.8 Hz, 2H), 7.9 (s, 1H), 7.6 (s, 1H), 3.7 (s, 3H), 3.0 (s, 3H), 2.95 (s, 3H). ES-LCMS m/z 333 (M^+).

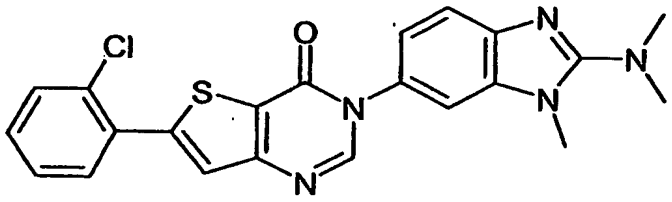


Step D: 3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]-6-(4-nitrophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

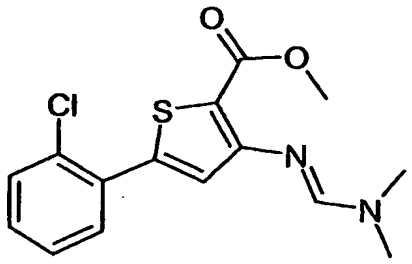
The title compound was prepared by reaction of methyl 3-{[(1*E*)-(dimethylamino)methylene]amino}-5-(4-nitrophenyl)thiophene-2-carboxylate (Step C above) (0.200 g, 0.60 mmol) with N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine (from Example 1, Step D) (0.114 g, 0.60 mmol) as described in Example 2, Step D. The crude product was triturated with

methanol to give 0.158 g (59% yield) of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.35 (d, J= 8.8 Hz, 2H), 8.23 (s, 1H), 8.21 (d, J= 8.8 Hz, 2H), 7.58 (m, 1H), 7.46 (m, 1H), 7.20 (m, 1H), 3.66 (s, 3H), 3.33 (s, 6 H). ES-LCMS m/z 447 $(M+H)^+$. The product was dissolved in dichloromethane, an excess of trifluoroacetic acid was added and the resulting solution was evaporated to dryness to afford 3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]-6-(4-nitrophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one as the trifluoroacetic acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.33 (d, J= 8.8 Hz, 2H), 8.24 (s, 1H), 8.21 (d, J= 8.8 Hz, 2H), 7.92 (m, 1H), 7.51 (m, 1H), 7.49 (m, 1H), 3.80 (s, 3H), 3.27 (s, 6H).

Example 33



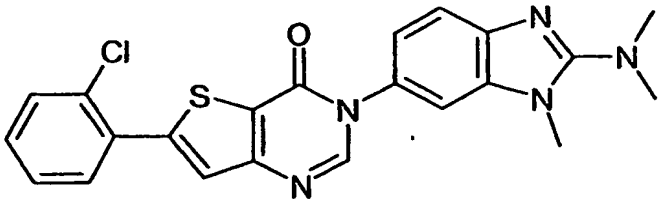
6-(2-Chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: methyl 5-(2-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate

Methyl 5-(2-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate was prepared as described in Example 32, Steps A through C, starting with 1-(2-chlorophenyl)ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.8 (s, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.4 (m, 2H), 7.2 (s, 1H), 3.7

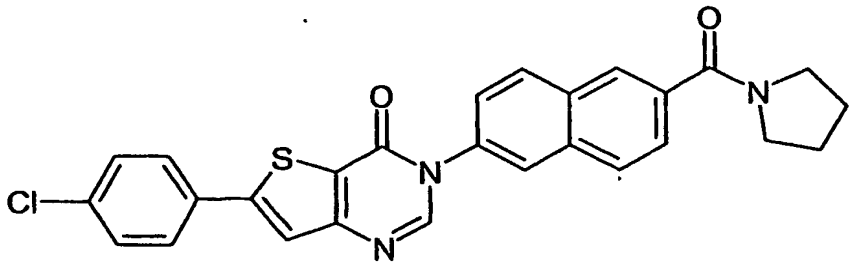
(s, 3H), 3.0 (s, 3H), 2.95 (s, 3H). ES-LCMS m/z 323 (M+H).



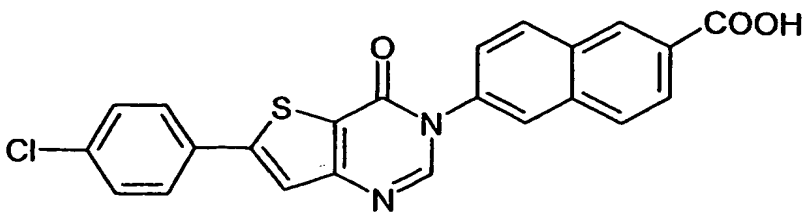
Step B: 6-(2-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared by reaction of methyl 5-(2-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Step A above) (0.311 g, 0.96 mmol) with N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine (from Example 11, Step D) (0.183 g, 0.96 mmol) as described in Example 2, Step D. The crude product was triturated with methanol, then suspended in dichloromethane and treated with an excess of trifluoroacetic acid. Diethyl ether was added and the precipitated trifluoroacetic acid salt was collected by filtration and dried under vacuum to give 0.185 g (35% yield) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.91 (s, 1H), 7.80 (s, 2H), 7.67 (m, 1H) 7.58 (m, 1H), 7.52 (m, 3H), 3.80 (s, 3H), 3.28 (s, 6H), ES-LCMS m/z 436 (M+H).

Example 34

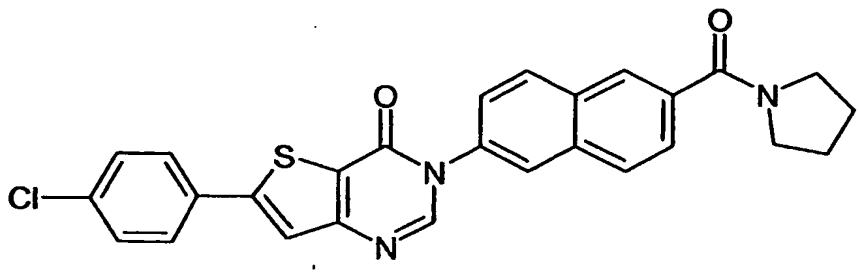


6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylcarbonyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-naphthalenecarboxylic acid

The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (from Example 1, Step D) (1.09 g, 3.38 mmol) and 6-amino-2-naphthalenecarboxylic acid (0.63 g, 3.38 mmol) as described in Example 2, Step D. The crude product was triturated with methanol and dried under vacuum to give 0.345 g (25% yield) of an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.60 (s, 1H), 8.28 (m, 1H), 8.23 (s, 1H), 8.09 (s, 2H), 8.03 (s, 1H), 7.96 (d, J= 8.6 Hz, 2H), 7.76 (m, 1H), 7.60 (d, J= 8.6 Hz, 2H).

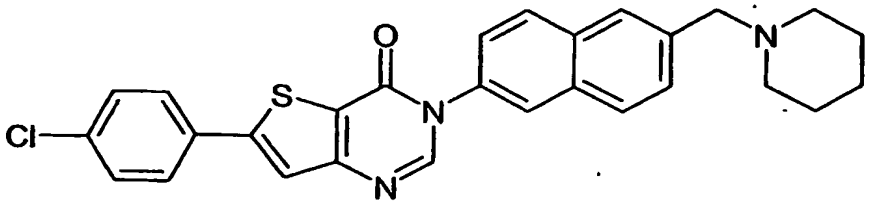


Step B: 6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylcarbonyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

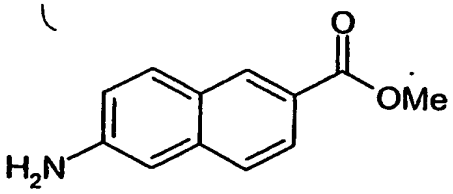
Oxalyl chloride (0.015 mL, 0.17 mmol) and a catalytic amound of N,N-dimethylformamide was added to a suspension of 6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-naphthalenecarboxylic acid (Step A above) (0.050 g, 0.12 mmol) in 2 mL of dichloromethane. The reaction mixture was stirred at room temperature for 30 minutes. The solvent was removed under vacuum and the residue was suspended in 2 mL of dichloromethane. Pyrrolidine (0.024 mL, 0.29 mmol) was added. The solvent

was evaporated and the residue was purified by chromatography on silica gel with a gradient of 0 to 10% methanol in dichloromethane to afford 0.020 g (36% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.21 (m, 2H), 8.17 (m, 1H), 8.05 (m, 1H), 8.01 (s, 1H), 7.94 (d, J= 8.6 Hz, 2H), 7.72 (m, 2H), 7.58 (d, J= 8.6 Hz, 2H), 3.52 (m, 2H), 3.46 (m, 2H), 1.90 (m, 2H), 1.83 (m, 2H). APCI-LCMS m/z 486 (M+H).

Example 35

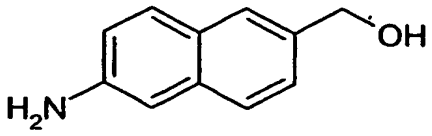


6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



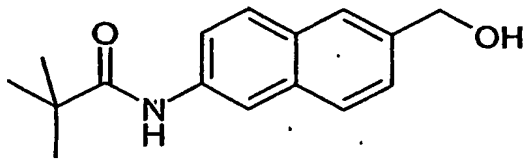
Step A: methyl 6-amino-2-naphthalenecarboxylate

A mixture of 6-amino-2-naphthalenecarboxylic acid (5.00 g, 26.7 mmol), 10 mL of concentrated sulfuric acid and 50 mL of methanol was heated at reflux for 1.5 hours. The reaction mixture was cooled to room temperature and poured into ice, then extracted with dichloromethane. The organic phase was dried over sodium sulfate and the solvent removed under vacuum to give 5.11 g (95% yield) of methyl 6-amino-2-naphthalenecarboxylate as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.79 (m, 2H), 7.57 (m, 1H), 7.05 (m, 1H), 6.86 (s, 1H), 5.88 (s, 2H), 3.88 (s, 3H).



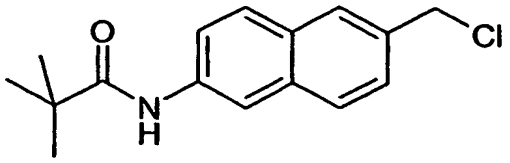
Step B: (6-amino-2-naphthalenyl)methanol

Lithium aluminum hydride (41 mL of a 1.0 M solution in tetrathydrofuran) was added to a solution of methyl 6-amino-2-naphthalenecarboxylate (5.11 g, 25.4 mmol) in 100 mL of anhydrous tetrahydrofuran while cooling in an ice bath. The mixture was stirred at 5 °C for 2 hours and quenched with 5 mL of water. The mixture was filtered and the filter cake was washed with tetrahydrofuran (4x30 mL). The combined filtrates were evaporated to dryness to give 4.06 g of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (m, 2H), 7.43 (m, 1H), 7.22(m, 1H), 6.88 (m, 1H), 6.77 (s, 1H), 5.28 (s, 2H), 5.08 (m, 1H), 4.51 (m, 2H).



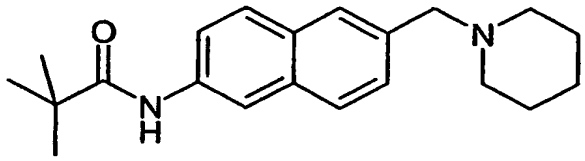
Step C: *N*-[6-(hydroxymethyl)-2-naphthalenyl]-2,2-dimethylpropanamide

Triethylamine (1.2 mL, 8.67 mmol) was added to a suspension of (6-amino-2-naphthalenyl)methanol (1.00 g, 5.78 mmol) in 60 mL of chloroform. The mixture was cooled in an ice bath and pivaloyl chloride (0.81 mL, 10.4 mmol) was added. The reaction mixture was stirred at 0 °C for one hour. After warming to room temperature, the mixture was diluted with chloroform and washed with 1N aqueous hydrochloric acid and water, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by chromatography on silica gel with hexane:ethyl acetate to give 1.22 g (80% yield) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.78 (m, 3H), 7.47 (m, 3H), 4.83 (s, 2H), 1.66 (br s, 1H), 1.36 (s, 9H).



Step D: *N*-[6-(Chloromethyl)-2-naphthalenyl]-2,2-dimethylpropanamide

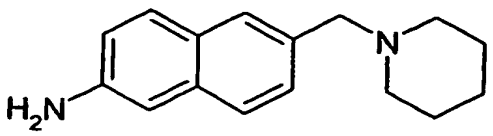
A mixture of 6.63 g of polystyrene-triphenylphosphine resin (1.35 mmol/g, 8.95 mmol), *N*-[6-(hydroxymethyl)-2-naphthalenyl]-2,2-dimethylpropanamide (1.15 g, 4.47 mmol) in 75 mL of carbon tetrachloride was heated at reflux for 30 minutes. The reaction mixture was cooled to room temperature and filtered. The resin on the filter was washed with 4x20 mL portions of dichloromethane, and the filtrates were combined and evaporated under vacuum to give 0.87 g (71% yield) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 4H), 7.46 (m, 2H), 7.23 and 7.05 (m, 1H), 4.74 (s, 2H), 1.41 and 1.36 (s, 9H).



Step E: 2,2-dimethyl-*N*-[6-(1-piperidinylmethyl)-2-naphthalenyl]propanamide

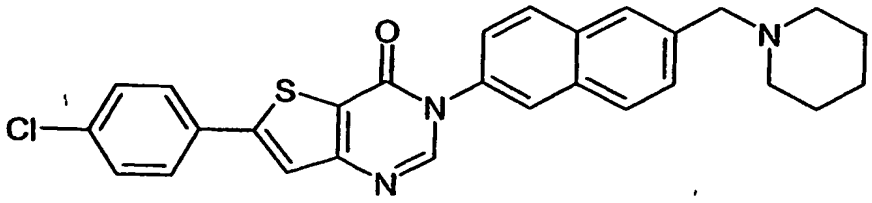
A mixture of *N*-[6-(chloromethyl)-2-naphthalenyl]-2,2-dimethylpropanamide, from Step D, (0.200 g, 0.73 mmol), piperidine (0.18 mL, 1.81 mmol) and 2 mL of tetrahydrofuran was heated at reflux for 1.5 hours. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with dichloromethane:methanol to give 0.089 g (38% yield) of the product as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.80 (m, 2H), 7.75 (s, 1H), 7.52 (s, 1H), 7.48 (m, 2H), 3.65 (s, 2H), 2.47 (m, 4H), 1.65 (m, 4H), 1.48 (m, 2H), 1.40 (s, 9H).

91



Step F: 6-(1-Piperidinylmethyl)-2-naphthalenamine

Aqueous hydrochloric acid (2 mL of a 2 N solution) was added to a suspension of 2,2-dimethyl-*N*-[6-(1-piperidinylmethyl)-2-naphthalenyl]propanamide from Step E above (0.089 g, 0.27 mmol) in 1 mL of ethanol. The resulting solution was heated in a microwave at 110 °C for 40 minutes. The cooled reaction mixture was neutralized with solid sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over sodium sulfate and the solvent was evaporated to give 0.041 g (63%yield) of 6-(1-piperidinylmethyl)-2-naphthalenamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 6.95 (m, 2H), 4.0 (br s, 2H), 3.61 (s, 2H), 2.46 (m, 4H), 1.61 (m, 4H), 1.44 (m, 2H).

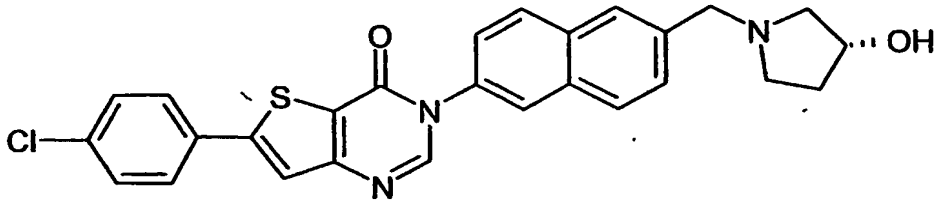


Step F: 6-(4-chlorophenyl)-3-[6-(1-piperidinylmethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

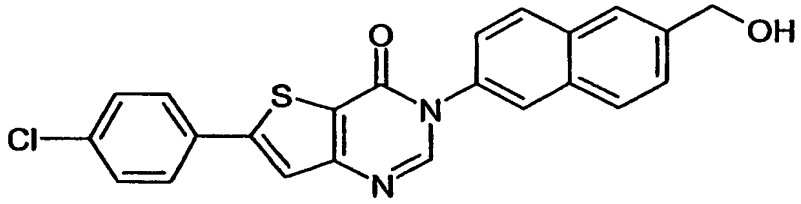
The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (from Example 1, Step D) (0.055 g, 0.17 mmol) and 6-(1-piperidinylmethyl)-2-naphthalenamine (Step E above) (0.041 g, 0.17 mmol) as described in Example 2, Step D. The crude product was triturated with methanol to give 0.040 g (48% yield) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s,

1H), 8.11 (s, 1H), 8.03 (m, 2H), 7.95 (m, 4H), 7.61 (m, 4H), 3.63 (s, 2H), 2.38 (m, 4H), 1.52 (m, 4H), 1.42 (m, 4H). Treatment with trifluoroacetic acid as described in Example 31, Step B, gave 0.035 g of the corresponding salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.58 (s, 1H), 8.18 (m, 4H), 8.05 (s, 1H), 7.97 (m, 1H), 7.79 (m, 2H), 7.60 (m, 2H), 4.52 (s, 2H), 3.41 (m, 2H), 2.95 (m, 2H), 1.82 (m, 2H), 1.70 (m, 2H), 1.40 (m, 1H), 1.07 (m, 1H). ES-LCMS m/z 486 (M+H).

Example 36

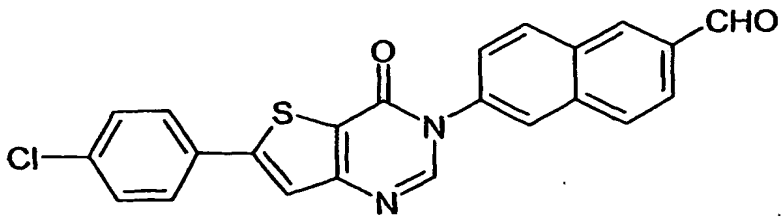


6-(4-chlorophenyl)-3-(6-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}-2-naphthalenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



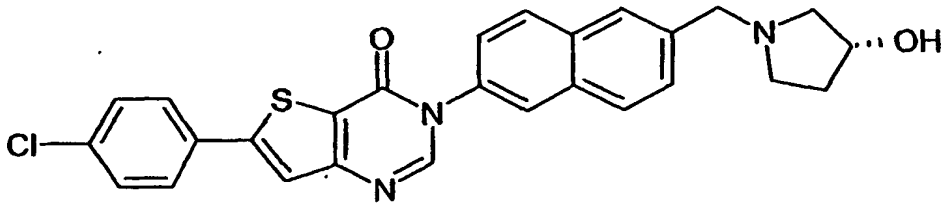
Step A: 6-(4-Chlorophenyl)-3-[6-(hydroxymethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (from Example 1, Step D) (1.86 g, 5.78 mmol) and (6-amino-2-naphthalenyl)methanol (from Example 35, Step B) (1.00 g, 5.78 mmol) as described in Example 2, Step D. The crude product was purified by trituration with methanol to give 1.20 g of a beige powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.12 (s, 1H), 8.07 (m, 1H), 8.03 (s, 1H), 7.96 (m, 4H), 7.59 (m, 4H), 5.43 (m, 1H), 4.73 (m, 2H).



Step B: 6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-naphthalenecarbaldehyde

A mixture of 6-(4-chlorophenyl)-3-[6-(hydroxymethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one, from Step A, (0.100 g, 0.24 mmol) and manganese dioxide (0.207 g, 2.4 mmol) in 30 mL of chloroform was stirred at room temperature for 24 hours. The reaction mixture was filtered through Celite and the solvent evaporated under vacuum to give 0.091 g (87% yield) of a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.70 (s, 1H), 8.60 (s, 1H), 8.34 (d, J= 8.8 Hz, 1H), 8.29 (s, 1H), 8.16 (d, J= 8.4 Hz, 1H), 8.0 (m, 2H), 7.93 (d, J= 8.4 Hz, 2H), 7.83 (d, J= 8.8 Hz, 1H), 7.56 (d, J= 8.6 Hz, 2H).

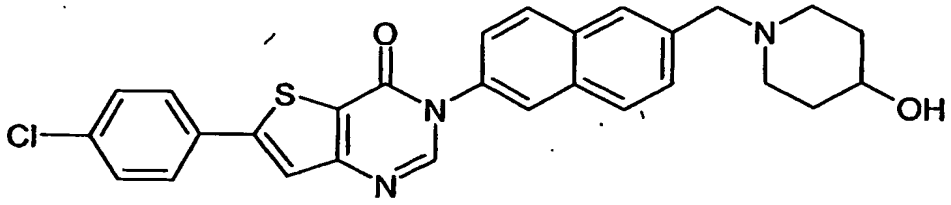


Step C: 6-(4-chlorophenyl)-3-(6-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}-2-naphthalenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

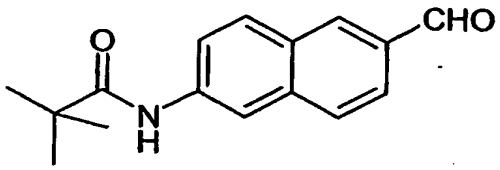
Sodium triacetoxyborohydride (0.117 g, 0.55 mmol) was added to a mixture of (3*R*)-3-pyrrolidinol (0.019 g, 0.22 mmol) and 6-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-naphthalenecarbaldehyde, from Step B, (0.091 g, 0.22 mmol) in 10 mL of dichloroethane. The reaction mixture was stirred at room temperature for 20 hours, filtered and the filtrate evaporated to dryness. The residue was purified by reverse phase HPLC on a C_{18} column

eluted with a gradient of 10 to 90% acetonitrile in 0.1% formic acid to give 0.013 g (12% yield) of the title compound as the formate salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.13 (s, 1H), 8.08 (d, J= 2.11 Hz, 1H), 8.02 (d, J= 9.0 Hz, 1H), 7.99 (s, 1H), 7.94 (m, 1H), 7.93 (d, J= 8.6 Hz, 2H), 7.90 (m, 1H), 7.62 (dd, J= 9.0 Hz, 2.11 Hz, 1H), 7.57 (d, J= 8.6 Hz, 2H), 4.68 (br s, 1H), 4.17 (m, 1H), 3.73 (m, 2H), 2.72 (m, 1H), 2.59 (m, 1H), 2.45 (m, 1H), 2.33 (m, 1H), 1.98 (m, 1H), 1.53 (m, 1H). ES-LCMS m/z 488 (M+H).

Example 37

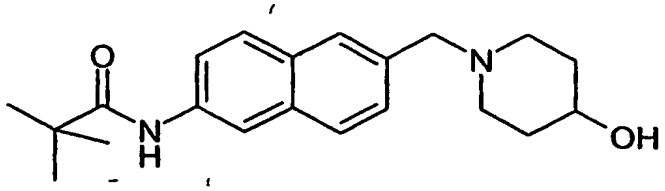


6-(4-chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



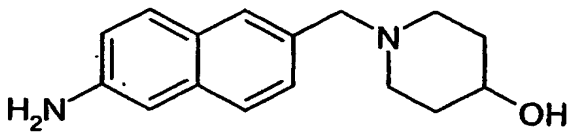
Step A: *N*-(6-formyl-2-naphthalenyl)-2,2-dimethylpropanamide

Reaction of *N*-[6-(hydroxymethyl)-2-naphthalenyl]-2,2-dimethylpropanamide (Example 35, Step C) (0.310 g, 1.20 mmol) with manganese dioxide (1.04 g, 12.0 mmol) following the procedure in Example 36, Step B gave 0.285 g (93% yield) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.37 (m, 1H), 8.27 (s, 1H), 7.96 (m, 2H), 7.92 (m, 1H), 7.56 (m, 2H), 1.38 (s, 9H). ES-LCMS m/z 256 (M+H).



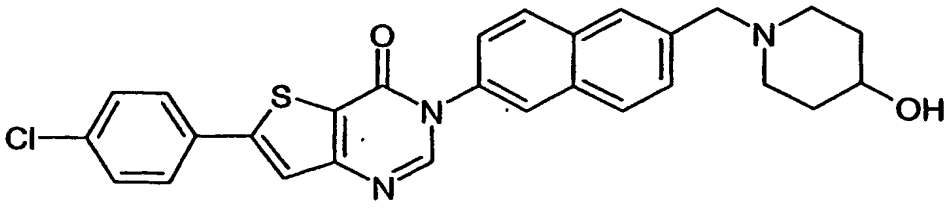
Step B: *N*-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}-2,2-dimethylpropanamide

The title compound was prepared by reaction of *N*-(6-formyl-2-naphthalenyl)-2,2-dimethylpropanamide (from Step A above) (0.259 g, 1.01 mmol) and 4-hydroxypiperidine (0.102 g, 1.01 mmol) with sodium triacetoxyborohydride as described in Example 36, Step C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.75 (m, 2H), 7.78 (m, 1H), 7.45 (m, 3H), 3.71 (br s, 1H), 3.65 (m, 2H), 2.79 (m, 2H), 2.22 (m, 1H), 1.91 (m, 2H), 1.60 (m, 4H), 1.37 (s, 9H).



Step C: 1-[(6-Amino-2-naphthalenyl)methyl]-4-piperidinol

The title compound was obtained from *N*-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}-2,2-dimethylpropanamide (Step B above) by the procedure in Example 35, Step F. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.57 (m, 2H), 7.36 (m, 1H), 6.97 (m, 1H), 6.94 (m, 1H), 3.82 (br s, 1H), 3.69 (br s, 2H), 3.60 (s, 2H), 2.79 (m, 2H), 2.18 (m, 2H), 1.89 (m, 2H), 1.61 (m, 2H).

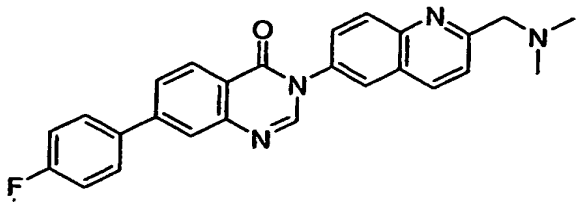


Step D: 6-(4-Chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

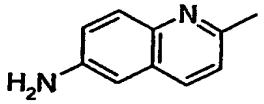
The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (from Example 1, Step D) (0.063 g, 0.195 mmol) and 1-[(6-amino-2-naphthalenyl)methyl]-4-piperidinol (Step C above) (0.050 g, 0.195 mmol) as

described in Example 2, Step D. The crude product was triturated with methanol/diethyl ether, then treated with trifluoroacetic acid as in Example 33 to give 0.030 g of the corresponding salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (br s, 1H), 8.58 (s, 1H), 8.22 (m, 1H), 8.14 (m, 2H), 8.04 (s, 1H), 7.96 (d, J= 8.4 Hz, 2H), 7.78 (m, 1H), 7.72 (m, 1H), 7.61 (d, J= 8.6 Hz, 2H), 5.05 (m, 1H), 4.5 (m, 2H), 3.2-3.4 (m, 4H), 3.05 (m, 1H), 2.0 (m, 1H), 1.95 (m, 2H), 1.61 (m, 1H).

Example 38

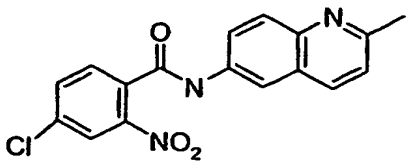


3-{2-[(dimethylamino)methyl]-6-quinolinyl}-7-(4-fluorophenyl)-4(3*H*)-quinazolinone



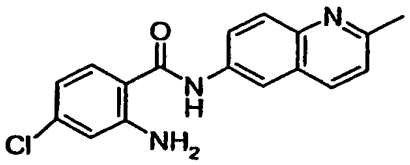
Step A: 2-methyl-6-quinolinamine

To a solution of 2-methyl-6-nitroquinoline (4.0 g, 21.3 mmol) in 150 mL ethyl alcohol, a catalytic amount of Pd/C was added. The mixture was stirred under 2 atm pressure of hydrogen in a Parr hydrogenation apparatus for 4 hours. The mixture was filtered through celite. After the solvent was removed under reduced pressure, 3.3 g of the product was collected as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.78 (m, 2H); 7.17-7.10(m, 2H); 6.87 (d, J = 2.8 Hz, 1H); 3.88 (bs, 2H); 2.66 (s, 3H). ES-LCMS *m/z* 159 (M+H).



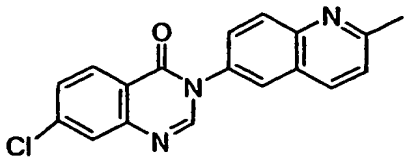
Step B: 4-chloro-*N*-(2-methyl-6-quinolinyl)-2-nitrobenzamide

A mixture of 2-methyl-6-quinolinamine (3.3 g, 20.8 mmol), triethylamine (5.9mL, 41.6mmol) and 4-chloro-2-nitrobenzoyl chloride (5.0 g, 22.9 mmol) in DCM (60 mL) was stirred at room temperature for 3 hours. The mixture was diluted with DCM, washed with saturated sodium bicarbonate solution, water and brine. After drying over sodium sulfate, the solvent was removed under reduced pressure. The residue obtained was purified by flash chromatography eluting with 10% acetone in DCM with 1% triethylamine. The product was obtained as a tan solid (2.8g). ^{1}H NMR (400 MHz, d_6-DMSO) δ 10.98 (s, 1H); 8.37(s, 1H); 8.28 (s, 1H); 8.21 (d, J = 8.4 Hz, 1H); 7.98 (d, J = 8.4Hz, 1H); 7.91-7.87 (m, 2H); 7.76 (d, J = 9.2 Hz, 2H); 7.38 (d, J = 8.4 Hz, 1H); 3.31 (s, 3H). ES-LCMS *m/z* 342 (M+H).



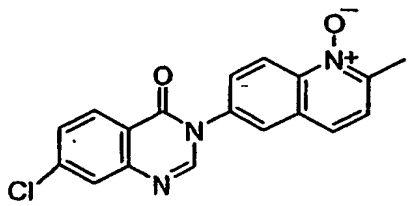
Step C: 2-amino-4-chloro-*N*-(2-methyl-6-quinolinyl)benzamide

To a boiling solution of 4-chloro-*N*-(2-methyl-6-quinolinyl)-2-nitrobenzamide (500 mg, 1.46 mmol) in ethyl alcohol (20 mL), tin chloride dihydrate (988 mg, 4.39 mmol) was added. The mixture was refluxed for 4 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate and then washed gently with saturated Rochelle salt solution numerous times before washing with brine. After drying, the solvent was removed and the product was collected as a foam (295 mg). ES-LCMS *m/z* 312 (M+H).



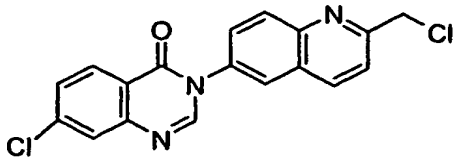
Step D: 7-chloro-3-(2-methyl-6-quinolinyl)-4(3*H*)-quinazolinone

2-Amino-4-chloro-*N*-(2-methyl-6-quinolinyl)benzamide (295 mg, 0.95 mmol) was dissolved in 5 mL formic acid and heated to reflux for 2 hours. The formic acide was then removed under reduced pressure and the residue was dissolved in ethyl acetate. The resultant solution was washed with water, saturated sodium bicarbonate solution, and brine. After removing the solvent at reduced pressure, the residue was purified by flash chromatography eluting with 10% acetone in DCM with 0.5% triethylamine. The product was obtained as an off white solid (265 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.4 Hz, 1H); 8.22 (s, 1H); 8.18 (d, J = 8.4 Hz, 1H); 8.10 (d, J = 8.4 Hz, 1H); 7.84 (s, 1H); 7.79 (s, 1H); 7.70 (d, J = 8.8 Hz, 1H); 7.52 (d, J = 8.4 Hz, 1H); 7.38 (d, J = 8.4 Hz, 1H); 2.79 (s, 3H). ES-LCMS *m/z* 322 (M+H).



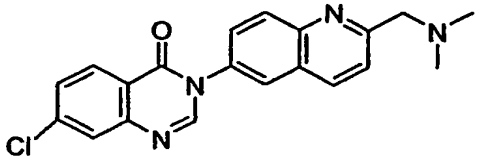
Step E: 7-chloro-3-(2-methyl-1-oxido-6-quinolinyl)-4(3*H*)-quinazolinone

To a solution of 7-chloro-3-(2-methyl-6-quinolinyl)-4(3*H*)-quinazolinone (530 mg, 1.65 mmol) in 30 mL DCM, *m*-CPBA (445 mg, 1.98 mmol) was added. The mixture was warmed to 40 °C and was stirred at this temperature overnight. The precipitate was collected by filtration. The solid was washed with a small amount of saturated sodium bicarbonate solution. The product was collected as a white solid (460 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, J = 9.2 Hz, 1H); 8.31 (d, J = 8.4 Hz, 1H); 8.20 (s, 1H); 7.94 (s, 1H); 7.81-7.77 (m, 2H); 7.69 (d, J = 8.4 Hz, 2H); 7.54 (d, J = 8.4 Hz, 1H); 7.43(d, J = 8.4 Hz, 1H); 2.76 (s, 3H). ES-LCMS *m/z* 338 (M+H).



Step F: 7-chloro-3-[2-(chloromethyl)-6-quinolinyl]-4(3*H*)-quinazolinone

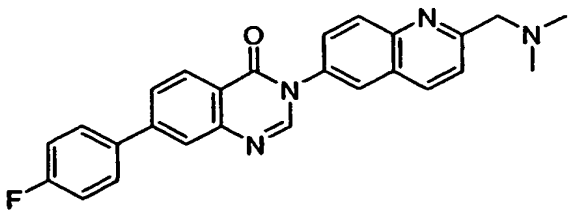
To a solution of p-toluenesulnonyl chloride (288 mg, 1.50 mmol) in 25 mL dichloroethane, 7-chloro-3-(2-methyl-1-oxido-6-quinolinyl)-4(3*H*)-quinazolinone (460 mg, 1.36 mmol) was added. The resulting mixture was heated to reflux for 40 hours. The solvent was removed under reduced pressure. The resulting residue was dissolved in DCM and washed with saturated sodium bicarbonate and brine. The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with 10% acetone in DCM with 1% triethylamine. The product was obtained as a white solid (235 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33-8.23 (m, 4H); 7.91(s, 1H); 7.80-7.76 (m, 2H); 7.72 (d, J = 8.8 Hz, 1H); 7.53 (d, J = 8.4 Hz, 2H); 4.87(s, 2H). ES-LCMS *m/z* 356 (M+H).



Step G: 7-chloro-3-{2-[(dimethylamino)methyl]-6-quinolinyl}-4(3*H*)-quinazolinone

A mixture of 7-chloro-3-[2-(chloromethyl)-6-quinolinyl]-4(3*H*)-quinazolinone (90 mg, 0.25 mmol) and excess dimethylamine (2 M solution in methanol) was stirred at room temperature overnight. The reaction mixture was diluted with DCM and washed with water and brine. After drying, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 10% acetone in DCM with 1% triethylamine. The product was obtained as a solid (76 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.4 Hz, 1H); 8.26-8.22 (m, 2H); 8.18 (d, J = 8.8 Hz, 1H); 7.86 (s, 1H);

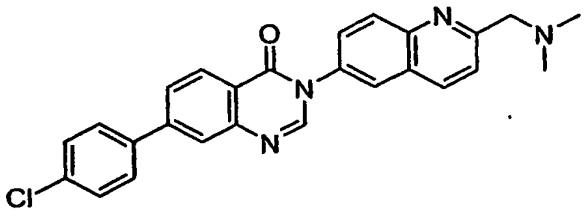
7.79 (s, 1H); 7.74-7.65 (m, 2H); 7.52 (d, J = 8.4 Hz, 1H); 3.80 (s, 2H); 2.34 (s, 6H). ES-LCMS *m/z* 365 (M+H).



Step H: 3-{2-[(dimethylamino)methyl]-6-quinolinyl}-7-(4-fluorophenyl)-4(3*H*)-quinazolinone

Under anhydrous conditions, 7-chloro-3-{2-[(dimethylamino)methyl]-6-quinolinyl}-4(3*H*)-quinazolinone (17 mg, 0.046 mmol), 4-fluorophenylboronic acid (13 mg, 0.093 mmol), potassium fluoride (8 mg, 0.14 mmol), di-tert-butylphosphinolbiphenyl (6 mg, 0.14mmol), and palladium acetate (3 mg, 0.01 mmol) in 1 mL THF was heated to 60 °C for 2 hours. The mixture was filtered and the filtrate was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 10% acetone in DCM with 1% triethylamine. The title compound was obtained as a white solid (12.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.4 Hz, 1H); 8.27-8.22 (m, 3H); 7.96 (s, 1H); 7.91 (s, 1H); 7.79-7.68 (m, 5H); 7.23-7.19 (m, 2H); 3.94(s, 2H); 2.46 (s, 6H). ES-LCMS *m/z* 425 (M+H).

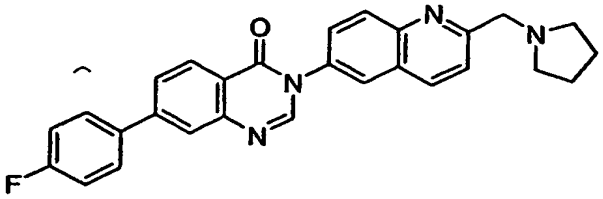
Example 39



7-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-6-quinolinyl}-4(3*H*)-quinazolinone

The title compound was synthesized by substituting 4-chlorophenylboronic acid for 4-fluorophenylboronic acid and employing the techniques found in Example 38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.4 Hz, 1H); 8.37-8.25 (m, 3H); 7.99 (s, 1H); 7.98 (s, 1H); 7.85-7.74 (m, 3H); 7.67 (d, J = 8.4 Hz, 1H); 7.50 (d, J = 8.4 Hz, 1H); 4.22 (bs, 2H); 2.72 (bs, 6H). ES-LCMS *m/z* 441 (M+H).

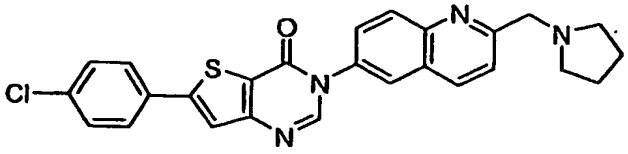
Example 40



7-(4-fluorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]-4(3*H*)-quinazolinone

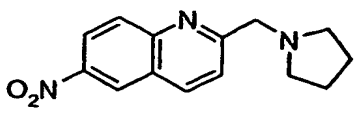
The title compound was synthesized by substituting pyrrolidine for dimethylamine and employing the techniques found in Example 38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48-8.44 (m, 2H); 8.38 (d, J = 8.0 Hz, 1H); 8.23 (d, J = 8.8Hz, 1H); 8.16 (s, 1H); 7.99 (s, 1H); 7.95-7.89 (m, 2H); 7.85-7.81 (m, 2H); 7.72 (d, J = 8.4 Hz, 1H); 7.27(m, 2H); 4.30 (s, 2H); 2.99(s, 4H); 1.99 (s, 4H). ES-LCMS *m/z* 451 (M+H).

Example 41



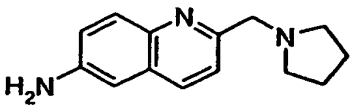
6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was synthesized by employing the techniques found in Example 1.



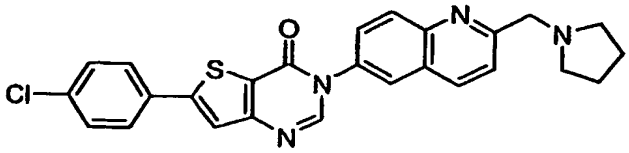
Step A: 6-nitro-2-(1-pyrrolidinylmethyl)quinoline

This intermediate was synthesized by substituting pyrrolidine for dimethylamine and employing the techniques found in Example 1, Step B. ^{1}H NMR (400 MHz, CDCL3) δ 8.75 (d, J = 2.4Hz, 1H); 8.43 (d, J = 9.2Hz, 1H); 8.28 (d, J = 8.8Hz, 1H); 8.18 (d, J = 9.6Hz, 1H); 7.77 (d, J = 8.4 Hz, 1H); 3.99(s, 2H); 2.64-2.61 (s, 4H); 1.85-1.81 (m, 4H). ES-LCMS *m/z* 258 (M+H).



Step B: 2-(1-pyrrolidinylmethyl)-6-quinolinamine

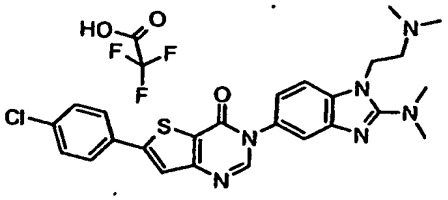
This intermediate was synthesized by employing the techniques found in Example 1, Step C. ^{1}H NMR (400 MHz, CDCL3) δ 7.87 (m, 2H); 7.49 (d, J = 8.4Hz, 1H); 7.12 (d, J = 8.4Hz, 1H); 6.88 (s, 1H); 3.92(s, 2H); 3.92 (bs, 1H); 2.66 (bs, 4H); 1.84-1.80 (m, 4H). ES-LCMS *m/z* 228 (M+H).



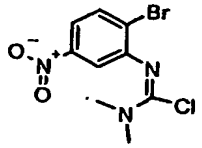
Step C: 6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-6-quinolinyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was synthesized by substituting 2-(1-pyrrolidinylmethyl)-6-quinolinamine for 2-[(dimethylamino)methyl]-6-quinolinamine and employing the techniques found in Example 1, step E. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.23 (m, 2H); 8.18 (d, J = 8.4Hz, 1H); 7.88 (d, J = 2.4Hz, 1H); 7.75-7.70 (m, 2H); 7.67 (d, J = 8.4 Hz, 2H); 7.56 (s, 1H); 7.45 (d, J = 8.8 Hz); 3.99(s, 2H); 2.63 (bs, 4H); 1.85-1.82 (m, 4H). ES-LCMS *m/z* 473 (M+H).

Example 42

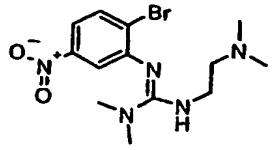


6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: *N'*-(2-bromo-5-nitrophenyl)-*N*,*N*-dimethylcarbamimidic chloride

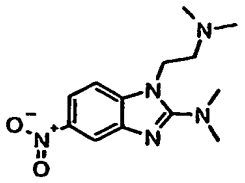
N-(Dichloromethylidene)-*N*-methylmethanaminium chloride (1.76 g, 10.8 mmol) and 2-bromo-5-nitroaniline (2.12 g, 9.79 mmol) were heated to reflux in methylene chloride (approximately 100 mL) for 16 hours. The reaction mixture was concentrated by rotary evaporation. The crude yellow solid was used without further purification.



Step B: *N'*-(2-Bromo-5-nitrophenyl)-*N''*-[2-(dimethylamino)ethyl]-*N*,*N*-dimethylguanidine

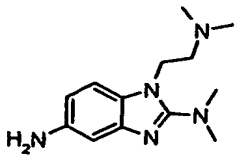
N'-(2-Bromo-5-nitrophenyl)-*N*,*N*-dimethylcarbamimidic chloride (the crude intermediate produced in Example 42, Step A; 600 mg, 1.9 mmol), triethylamine (272 µl, 0.727 mmol) and *N*,*N*-dimethyl-1,2-ethanediamine (645 µl, 5.88 mmol) were heated at reflux in THF (approximately 50 mL) for 14

hours. The reaction mixture was diluted with water, made basic with 1 N NaOH then extracted with ethyl acetate. The organic layers were dried over $MgSO_4$, filtered and concentrated to give desired intermediate (690 mg, 1.9 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 2.2 (s, 6 H) 2.4 (m, 2 H) 2.9 (s, 6 H) 3.0 (m, 2 H) 7.5 (dd, *J*=8.6, 2.6 Hz, 1 H) 7.6 (m, 2 H). ES+ = 358.28 and 360.19



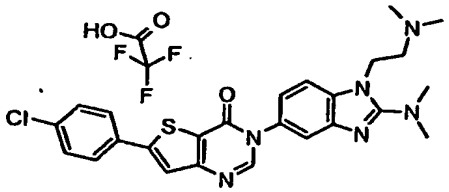
Step C: 1-[2-(Dimethylamino)ethyl]-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine

(*R*)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthly (BINAP) (124 mg, 0.195 mmol) and cesium carbonate (899 mg, 2.77 mmol) were added to a THF (approximately 25 mL) solution of *N'*-(2-bromo-5-nitrophenyl)-*N''*-[2-(dimethylamino)ethyl]-*N*,*N*-dimethylguanidine (the intermediate produced in Example 42, Step B; 395 mg, 0.06 mmol). The reaction flask was flushed with dry nitrogen. $Pd(OAc)_2$ (30 mg, 0.134 mmol) was added and the reaction was heated at 75 °C for 14 hours. The reaction was incomplete by HPLC so additional portions of $Pd(OAc)_2$ (30 mg, 0.134 mmol) and BINAP (124 mg, 0.195 mmol) were added until the reaction was complete (in this case only one additional portion of each was necessary). After heating at 75 °C for an additional 24 hours the reaction appeared complete by HPLC. The reaction was diluted with water and made acidic with 1N HCl. A precipitate was filtered away and the filtrate was made basic with 1N NaOH. This mixture was extracted with ethyl acetate (2x). The organic layer was dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (0 to 5% methanolic 2N NH_3 in methylene chloride) to give the desired intermediate (165 mg, 0.60 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 2.3 (s, 6 H) 2.7 (t, *J*=7.6 Hz, 2 H) 3.1 (s, 6 H) 4.2 (t, *J*=7.4 Hz, 2 H) 7.2 (d, *J*=8.8 Hz, 1 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.4 (d, *J*=2.2 Hz, 1 H). ES+ = 278.26



Step D: 1-[2-(dimethylamino)ethyl]-N^2,N^2-dimethyl-1*H*-benzimidazole-2,5-diamine

An ethyl acetate (approximately 60 mL) solution of 1-[2-(dimethylamino)ethyl]-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine (the intermediate produced in Example 42, Step C; 110 mg, 0.38 mmol) was shaken with approximately 50 mg 10% Pd on Carbon at 40 PSI on a Parr hydrogenator for 15 minutes. The reaction was filtered and concentrated to give the desired intermediate (100 mg, 0.46 mmol).

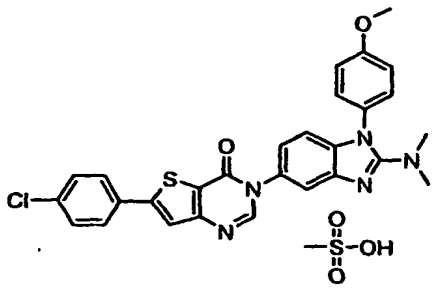


Step E: 6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

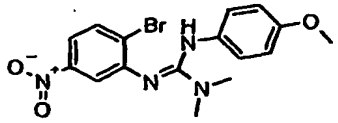
A solution of 1-[2-(dimethylamino)ethyl]-N^2,N^2-dimethyl-1*H*-benzimidazole-2,5-diamine amine (the intermediate produced in Example 42, step D; 100 mg, 0.46 mmol) in 2 mL of methylene chloride was added to a test tube containing 1 g of phenol and methyl 5-(4-chlorophenyl)-3-{[(E)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (the intermediate produced in Example 1, Step D; 148 mg, 0.46 mmol). The reaction mixture was heated in an aluminum heat block from room temperature to 180 °C for 30 minutes. The reaction mixture was allowed to cool then dissolved in methanol and absorbed onto silica. The product was purified by silica gel column chromatography (0 to 10% methanolic 2 N NH_3 solution in methylene chloride). This compound was further purified by preparative HPLC

chromatography (20% to 70% acetonitrile in water over 5 minutes) then lyophilized to give the title compound as a white powder (25 mg, 0.05 mmol). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 2.9 (s, 6 H) 3.2 (s, 6 H) 3.6 (t, *J*=7.4 Hz, 2 H) 4.6 (t, *J*=7.1 Hz, 2 H) 7.5 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.7 (d, *J*=2.1 Hz, 1 H) 7.8 (d, *J*=8.6 Hz, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 10.2 (s, 1 H). ES+ = 493.4

Example 43



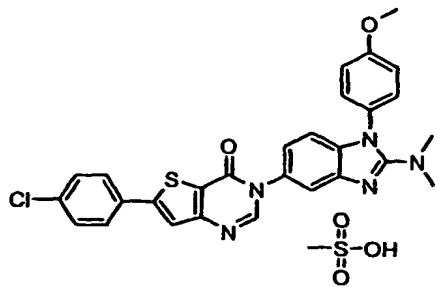
6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[4-(methyloxy)phenyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate



Step A: *N'*-(2-bromo-5-nitrophenyl)-*N*,*N*-dimethyl-*N''*-[4-(methyloxy)phenyl]guanidine

A solution of *N*,*N*-dimethyl-*N'*-[4-(methyloxy)phenyl]urea (0.50 g, 2.57 mmol), 2-bromo-5-nitroaniline (0.5 g, 2.3 mmol), $POCl_3$ (360 µl, 3.86 mmol) and triethylamine (393 µl, 2.8 mmol) in toluene (approximately 50 mL) was heated at 110 °C in toluene for 14 hours. The reaction mixture was concentrated by rotary evaporation. The solid was partially re-dissolved in ethyl acetate. Water and 1 N NaOH (to pH >10) were added and solid material that did not dissolve was filtered away. The filtrate was extracted with ethyl acetate (3x), dried over $MgSO_4$ and concentrated. This material was further purified by silica gel column chromatography (0 to 10% methanolic 2N NH_3 solution in

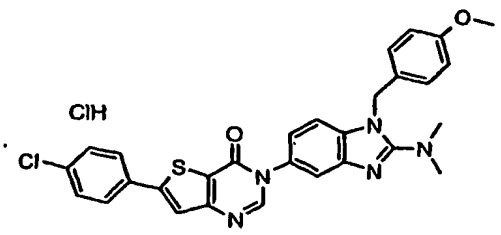
methylene chloride) to give the desired intermediate (475 mg, 1.21 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.0 (s, 6 H) 3.7 (s, 3 H) 6.7 (d, *J*=9.0 Hz, 2 H) 6.9 (d, *J*=8.8 Hz, 2 H) 7.5 (dd, *J*=8.8, 2.6 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 1 H) 7.7 (m, 1 H). ES+ = 393.16 and 395.18



Step B: 6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[4-(methyloxy)phenyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

The title compound was prepared from *N'*-(2-bromo-5-nitrophenyl)-*N*,*N*-dimethyl-*N"*-[4-(methyloxy)phenyl]guanidine (the intermediate produced in Example 43, step A) using experimental procedures similar to Example 42, Steps C, D and E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (s, 3 H) 2.9 (s, 6 H) 3.9 (s, 3 H) 7.0 (d, *J*=8.6 Hz, 1 H) 7.2 (d, *J*=8.8 Hz, 2 H) 7.3 (m, 1 H) 7.6 (m, 5 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES+ = 528.16

Example 44

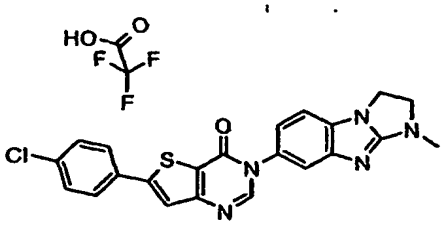


6-(4-chlorophenyl)-3-(2-(dimethylamino)-1-{[4-(methyloxy)phenyl]methyl}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride

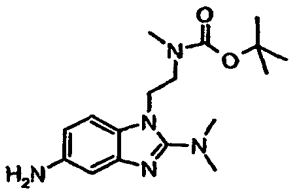
The title compound was prepared by substituting 1-[4-(methyloxy)phenyl]-methanamine for *N*,*N*-dimethyl-1,2-ethanediamine using the methods detailed

in Example 42, Steps B through E. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 3.2 (s, 6 H) 3.7 (s, 3 H) 5.5 (s, 2 H) 6.9 (d, *J*=8.8 Hz, 2 H) 7.2 (d, *J*=8.6 Hz, 2 H) 7.4 (m, 1 H) 7.5 (m, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.7 (m, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES+ = 542.25

Example 45



6-(4-chlorophenyl)-3-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



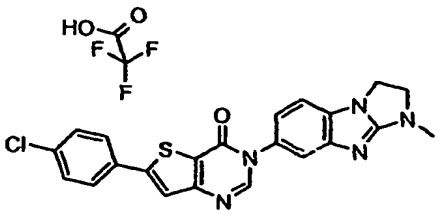
Step A: 1,1-Dimethylethyl {2-[5-amino-2-(dimethylamino)-1*H*-benzimidazol-1-yl]ethyl}methylcarbamate

This intermediate was prepared using similar experimental procedures as in Example 42, step B (substituting 1,1-dimethylethyl (2-aminoethyl)methylcarbamate for *N*,*N*-dimethyl-1,2-ethanediamine), step C and step D. This intermediate was used without further purification.

Step B: A mixture of two products

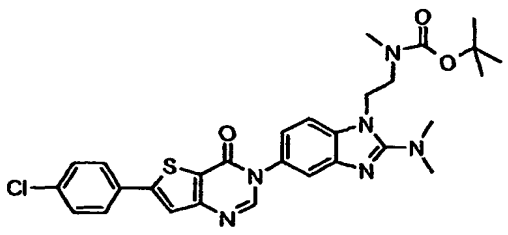
1,1-Dimethylethyl {2-[5-amino-2-(dimethylamino)-1*H*-benzimidazol-1-yl]ethyl}-methylcarbamate (the intermediate produced in Example 45, step A; 94 mg, 0.30 mmol) and methyl 5-(4-chlorophenyl)-3-{[(E)-(dimethylamino)-methylidene]amino} -2-thiophenecarboxylate (the intermediate produced in

Example 1, step D; 100 mg, 0.31 mmol) were combined using the experimental procedure as in Example 42 step E to give two compounds.



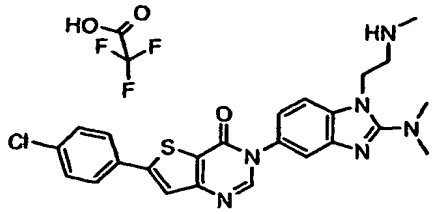
Example 45, Step B, Product 1: (6-(4-chlorophenyl)-3-(1-methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate)

The title compound was isolated by preparative HPLC (6 mg, 0.012 mmol): ^{1}H NMR (400 MHz, DMSO-*d*6) δ 3.1 (s, 3 H) 4.2 (m, 2 H) 4.3 (m, 2 H) 7.3 (m, 1 H) 7.5 (m, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.6 (m, 1 H) 7.9 (d, *J*=8.4 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES+ = 434.15



Example 45, Step B, product 2: 1,1-dimethylethyl {2-[5-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-(dimethylamino)-1*H*-benzimidazol-1-yl]ethyl}methylcarbamate Approximately 5 mg of this intermediate was carried on to Example 46.

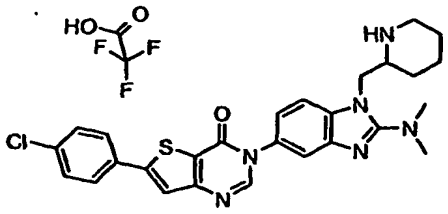
Example 46



6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methylamino)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

1,1-Dimethylethyl {2-[5-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-(dimethylamino)-1*H*-benzimidazol-1-yl]ethyl}methylcarbamate (Example 45, Step B product 2; 5 mg) was dissolved in 1 mL methylene chloride and 1 mL TFA. After 30 minutes the reaction was concentrated to give 3 mg of the title compound. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 2.7 (t, *J*=5.2 Hz, 2 H) 3.2 (s, 6 H) 3.4 (m, 2 H) 4.5 (t, *J*=7.4 Hz, 2 H) 7.5 (m, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.7 (d, *J*=1.9 Hz, 1 H) 7.7 (d, *J*=8.8 Hz, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 8.7 (s, 2 H). ES+ = 479.25

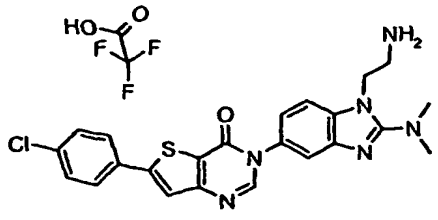
Example 47



6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-piperidinylmethyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was prepared using experimental procedures similar to Example 42, Step B (substituting 1,1-dimethylethyl 2-(aminomethyl)-1-piperidinecarboxylate for *N*,*N*-dimethyl-1,2-ethanediamine), Example 42, Steps C through E and the amine deprotection employed in Example 46. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.6 (m, 6 H) 3.0 (s, 6 H) 4.4 (m, 2 H) 7.3 (m, 1 H) 7.6 (m, 4 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 8.5 (m, 1 H) 8.7 (m, 1 H). ES+ = 519.21

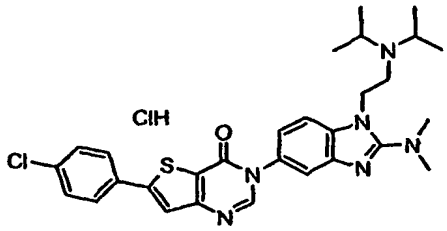
Example 48



3-[1-(2-aminoethyl)-2-(dimethylamino)-1*H*-benzimidazol-5-yl]-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was prepared using experimental procedures similar to Example 42, Step B (substituting 1,1-dimethylethyl (2-aminoethyl)carbamate for *N*,*N*-dimethyl-1,2-ethanediamine), Example 42 steps C through E and the amine deprotection employed in Example 46. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.9 (s, 6 H) 3.2 (t, *J*=7.3 Hz, 1 H) 4.3 (t, *J*=7.9 Hz, 2 H) 7.2 (dd, *J*=8.2, 1.8 Hz, 1 H) 7.5 (d, *J*=8.4 Hz, 1 H) 7.6 (d, *J*=2.2 Hz, 1 H) 7.6 (m, 2 H) 7.9 (m, 4 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES+ = 465.08

Example 49

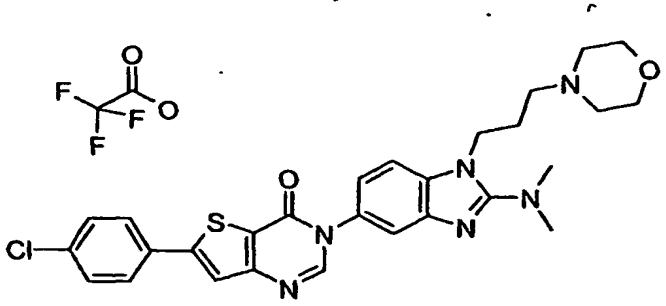


3-[1-{2-[bis(1-methylethyl)amino]ethyl}-2-(dimethylamino)-1*H*-benzimidazol-5-yl]-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride

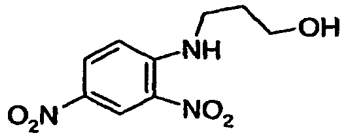
The title compound was prepared using experimental procedures similar to Example 42, Step B (substituting *N*,*N*-bis(1-methylethyl)-1,2-ethanediamine for *N*,*N*-dimethyl-1,2-ethanediamine) and Example 42 steps C through E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.3 (d, *J*=6.4 Hz, 6 H) 1.4 (d, *J*=6.6 Hz, 6 H) 3.2 (s: br, 6 H) 3.4 (m, 2 H) 3.8 (m, 2 H) 4.8 (m, 2 H) 7.4 (m, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.7 (m, 1 H) 7.8 (m, 1 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H).

ES+ = 548.78

Example 50

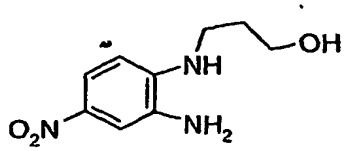


6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-morpholin-4-ylpropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 3-[(2,4-dinitrophenyl)amino]propan-1-ol

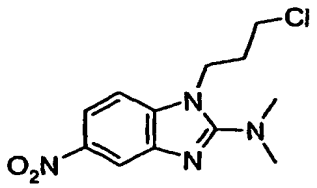
A solution of 3-amino-1-propanol (7.86 mL, 103 mmol) in ethanol (30 mL) was treated with triethylamine (14.3 mL, 103 mmol), followed by dropwise addition of 2,4-dinitrofluorobenzene (8.6 mL, 69 mmol). The reaction mixture was stirred for one hour and then heated in a sealed tube at 80 °C overnight. Concentration, followed by column chromatography on silica get using methylene chloride afforded 3-[(2,4-dinitrophenyl)amino]propan-1-ol as a yellow solid (14.3 g, 86%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 3.6 (m, 4 H) 4.8 (s, 1 H) 7.2 (d, *J*=9.7 Hz, 1 H) 8.3 (ddd, *J*=9.7, 2.8, 0.8 Hz, 1 H) 8.9 (d, *J*=2.8 Hz, 1 H) 9.1 (m, 1 H).



Step B: 3-[(2-amino-4-nitrophenyl)amino]propan-1-ol

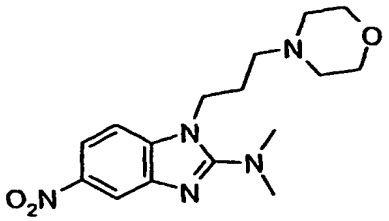
A solution of sodium dithionite (28.9 g, 166 mmol) in water (100 mL) was

added slowly to a solution of 3-[(2,4-dinitrophenyl)amino]propan-1-ol (the intermediate produced in Example 50, Step A; 10.0 g, 41.5 mmol) in ethanol:dioxane (160:160 mL) at 40 °C. The reaction mixture was warmed to 80 °C, stirred for 90 minutes, and then cooled to room temperature. The solids were filtered and solution was concentrated. The residue was taken up in water and washed with dichloromethane. The combined organics were dried and the solvent was removed *in vacuo*. The residue was recrystalized from methanol:dichloromethane to yield 3-[(2-amino-4-nitrophenyl)amino]propan-1-ol as a brown solid (3.11 g, 36% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.7 (m, 2 H) 3.2 (m, 2 H) 3.5 (m, 2 H) 4.5 (m, 1 H) 5.1 (m, 2 H) 5.9 (m, 1 H) 6.5 (d, *J*=9.0 Hz, 1 H) 7.4 (dd, *J*=2.8 Hz, 1 H) 7.5 (dd, *J*=8.8, 2.6 Hz, 1 H).



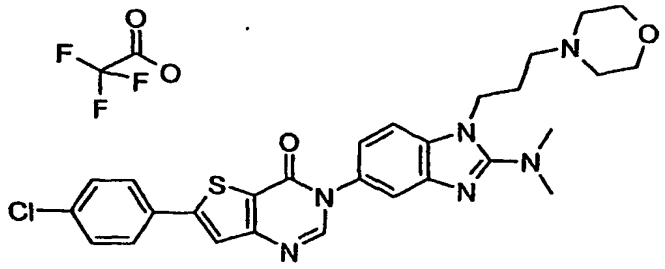
Step C: 1-(3-chloropropyl)-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine

Phosgene iminium chloride (693 mg, 4.27 mmol) was added to a solution of triethylamine (792 µL, 5.68 mmol) and 3-[(2-amino-4-nitrophenyl)amino]propan-1-ol (the intermediate produced in Example 50, Step B; 300 mg, 1.42 mmol) in dichloroethane (18 mL) at 80 °C. The reaction mixture was stirred at reflux for 25 minutes, cooled to room temperature and quenched with methanol. The reaction was diluted with dichloromethane, washed with brine, dried, and concentrated. The residue was purified on silica gel (0-8% MeOH/CH_2Cl_2) to afford 1-(3-chloropropyl)-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine as a tan solid (250 mg, 62 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.3 (m, 2 H) 3.1 (m, 6 H) 3.5 (t, *J*=5.9 Hz, 2 H) 4.3 (m, 2 H) 7.2 (d, *J*=8.8 Hz, 1 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.4 (d, *J*=2.1 Hz, 1 H). LCMS m/z = 283 (m + H^+).



Step D: *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine

A solution of 1-(3-chloropropyl)-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine (the intermediate produced in Example 50, Step C; 122 mg, 0.432 mmol) in THF (6 mL) was treated with excess morpholine, followed by excess potassium carbonate. The reaction was heated at 90 °C in a sealed tube for two days. The reaction mixture was cooled to room temperature, concentrated, dissolved in dichloromethane, washed with brine, and extracted with dichloromethane. The combined organics were dried and chromatographed on silica gel (0-5% 2.0 N NH_3 in MeOH/CH_2Cl_2) to provide *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine as a yellow oil (142 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.0 (m, 2 H) 2.3 (t, *J*=6.6 Hz, 2 H) 2.3 (m, 4 H) 3.0 (m, 6 H) 3.7 (m, 4 H) 4.2 (t, *J*=7.2 Hz, 2 H) 7.2 (d, *J*=8.8 Hz, 1 H) 8.0 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.4 (d, *J*=2.2 Hz, 1 H). LCMS m/z = 334 (m + H^+).

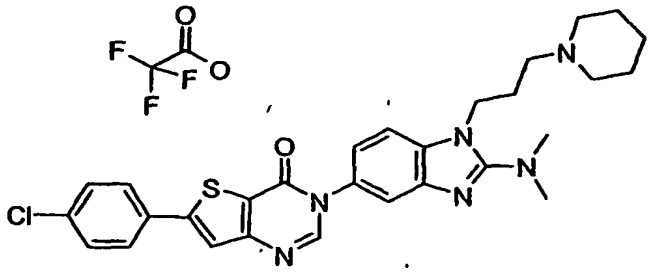


Step E: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-morpholin-4-ylpropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

N,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine (the intermediate produced in Example 50, Step D; 152 mg, 0.456 mmol) in ethanol was treated with a catalytic amount of Pd/C (10%) and stirred under

hydrogen gas (40 psi) for one hour. The reaction mixture was filtered through Celite and concentrated. This crude material was treated with methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (the intermediate produced in Example 1, Step D; 155 mg, 0.479 mmol) in phenol (1 mL) and dichloromethane (4 mL), warmed to 130 °C and stirred for ~30min. The reaction was cooled and purified on silica gel (0-5% 2.0 N NH_3 in $MeOH/CH_2Cl_2$). The compound was dissolved in dichloromethane, treated with two equivalents of trifluoroacetic acid and concentrated to provide 231 mg of 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-morpholin-4-ylpropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate (the title compound) as a white solid. ^{1}H NMR (TFA salt, 300 MHz, DMSO-d_6) δ 2.2 (m, 2 H) 3.1 (m, 2 H) 3.2 (m, 6 H) 3.3 (m, 2 H) 3.4 (m, 2 H) 3.6 (m, 2 H) 4.0 (m, 2 H) 4.3 (t, *J*=8.6 Hz, 2 H) 7.4 (d, *J*=8.0 Hz, 1 H) 7.6 (dt, *J*=8.6, 2.8 Hz, 2 H) 7.7 (d, *J*=1.7 Hz, 1 H) 7.7 (d, *J*=8.6 Hz, 1 H) 7.9 (dt, *J*=8.8, 2.5 Hz, 2 H) 8.4 (s, 1 H) 9.9 (bs, 1 H). APCI-LCMS m/z = 549 (m + H^+).

Example 51

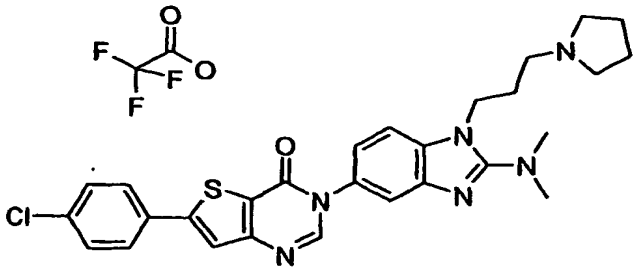


6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-piperidin-1-ylpropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting piperadine for morpholine and employing the techniques found in Example 50, Steps D and E. ^{1}H NMR (TFA salt, 300 MHz, DMSO-d_6) δ 1.4 (m, 1 H) 1.6 (m, 3 H) 1.8 (m, 2 H) 2.2 (m, 2 H) 2.9 (m, 2 H) 3.1 (m, 6 H) 3.2 (m, 2 H) 3.4 (m, 2 H) 4.3 (m, 2 H) 7.4 (d, *J*=8.3 Hz, 1 H) 7.6 (m, 2 H) 7.6 (d, *J*=1.9 Hz, 1 H) 7.7 (d, *J*=8.3 Hz, 1 H) 7.9 (s, 2 H) 8.0 (m, 1 H) 8.4 (s, 1 H) 9.2 (bs, 1 H). APCI-LCMS m/z = 547 (m +

H^+).

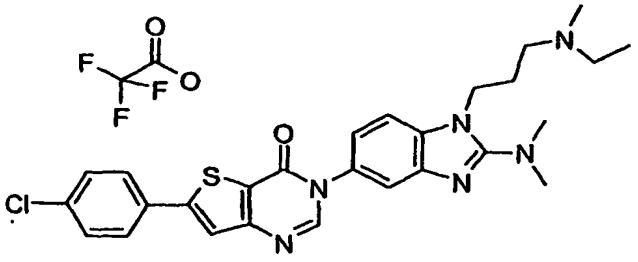
Example 52



6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-pyrrolidin-1-ylpropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting pyrrolidine for morpholine and employing the techniques found in Example 50, Steps D and E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 1.9 (m, 2 H) 2.0 (m, 2 H) 2.2 (m, 2 H) 3.0 (m, 2 H) 3.2 (m, 6 H) 3.3 (m, 2 H) 3.5 (m, 2 H) 4.3 (t, *J*=7.4 Hz, 2 H) 7.4 (d, *J*=9.1 Hz, 1 H) 7.6 (dt, *J*=8.6, 1.9 Hz, 2 H) 7.7 (d, *J*=1.9 Hz, 1 H) 7.7 (d, *J*=8.4 Hz, 1 H) 7.9 (dt, *J*=8.8, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.9 (bs, 1 H). APCI-LCMS m/z = 533 (m + H^+).

Example 53

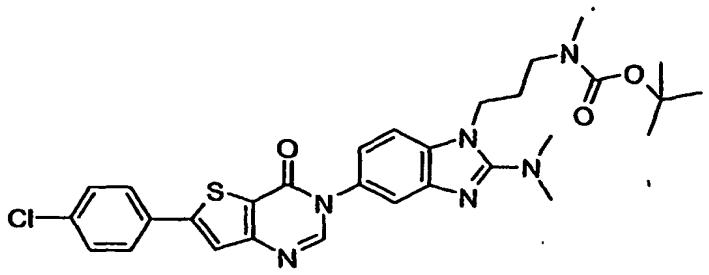


6-(4-chlorophenyl)-3-(2-(dimethylamino)-1-{3-[ethyl(methyl)amino]propyl}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

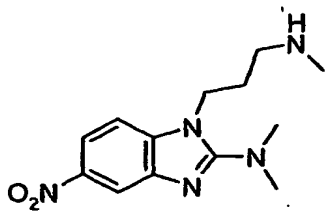
The title compound was synthesized by substituting N-ethylmethylamine for morpholine and employing the techniques found in Example 50, Steps D and

E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 1.2 (t, *J*=7.2 Hz, 3 H) 2.1 (m, 2 H) 2.7 (d, *J*=5.0 Hz, 3 H) 3.1 (m, 2 H) 3.2 (s, 6 H) 3.2 (m, 2 H) 4.3 (t, *J*=7.9 Hz, 2 H) 7.4 (d, *J*=7.2 Hz, 1 H) 7.6 (dt, *J*=8.8, 2.2 Hz, 2 H) 7.6 (d, *J*=1.7 Hz, 1 H) 7.7 (d, *J*=8.1 Hz, 1 H) 7.9 (dt, *J*=8.8, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.4 (bs, 1 H). APCI-LCMS m/z = 521 (m + H$^+$).

Example 54

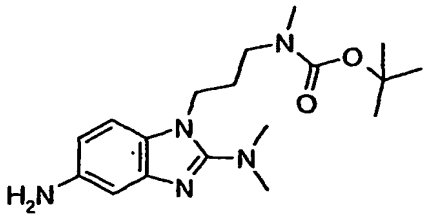


***tert*-butyl {3-[5-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-(dimethylamino)-1*H*-benzimidazol-1-yl]propyl}methylcarbamate**



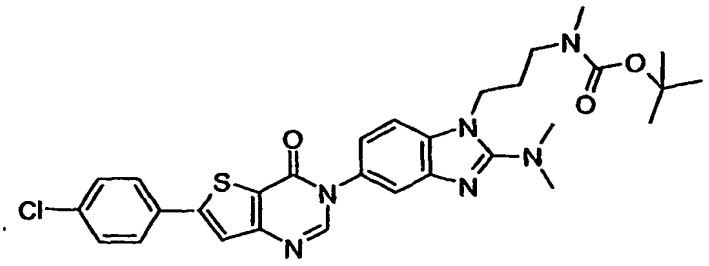
Step A: *N*,*N*-dimethyl-1-[3-(methylamino)propyl]-5-nitro-1*H*-benzimidazol-2-amine

The title compound was synthesized by substituting methylamine for morpholine and employing the techniques found in Example 50, Step D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (m, 2 H) 2.4 (s, 3 H) 2.6 (t, *J*=6.6 Hz, 2 H) 3.1 (s, 6 H) 4.2 (m, 2 H) 7.3 (d, *J*=8.8 Hz, 1 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.4 (d, *J*=2.2 Hz, 1 H). APCI-LCMS m/z = 278 (m + H$^+$).



Step B: *tert*-butyl {3-[5-amino-2-(dimethylamino)-1*H*-benzimidazol-1-yl]propyl}methylcarbamate

N,*N*-Dimethyl-1-[3-(methylamino)propyl]-5-nitro-1*H*-benzimidazol-2-amine (the intermediate produced in Example 54, Step A; 87 mg, 0.31 mmol) in ethanol was treated with a catalytic amount of Pd/C (10%) and stirred under hydrogen gas (40 psi) for one hour. The reaction mixture was filtered through Celite and concentrated. This crude material was taken up in dichloromethane, treated with di-*tert*-butyl dicarbonate (69 mg, 0.31 mmol). The reaction mixture was stirred for one hour and then purified on silica gel (0-10% 2 N NH_3 in MeOH/CH_2Cl_2) to provide the title compound (50 mg, 46% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 1.5 (s, 9 H) 2.0 (m, 2 H) 2.8 (s, 3 H) 3.0 (s, 6 H) 3.3 (m, 2 H) 3.6 (m, 2 H) 4.0 (m, 2 H) 6.6 (dd, *J*=8.3, 2.2 Hz, 1 H) 6.9 (m, 2 H). APCI-LCMS m/z = 348 ($m + H^+$).

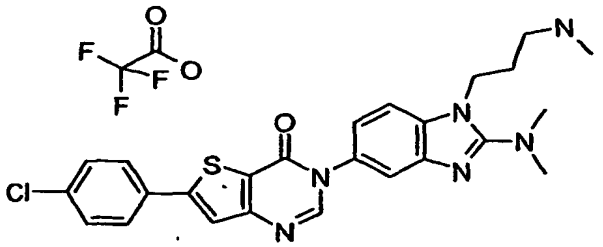


Step C: *tert*-butyl {3-[5-[6-(4-chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-(dimethylamino)-1*H*-benzimidazol-1-yl]propyl}methylcarbamate

A solution of *tert*-butyl {3-[5-amino-2-(dimethylamino)-1*H*-benzimidazol-1-yl]propyl}methylcarbamate (the intermediate produced in Example 54, Step B; 50 mg, 0.14 mmol) in phenol (1 mL) and dichloromethane (5 mL) was treated with the intermediate produced in Example 1, Step D (51 mg, 0.16 mmol), heated to 100 °C, and stirred for 30 minutes. The reaction was cooled and

purified on silica gel (0-10% 2.0 N NH_3 in $MeOH/CH_2Cl_2$) to provide the title compound as a white solid (29 mg). ^1H NMR (TFA salt, 400 MHz, $CDCl_3$) δ 1.5 (s, 9 H) 2.1 (m, 2 H) 2.9 (m, *J*=17.8 Hz, 3 H) 3.1 (s, 6 H) 3.3 (s, 2 H) 4.1 (t, *J*=7.9 Hz, 2 H) 7.2 (d, *J*=7.9 Hz, 1 H) 7.3 (d, *J*=8.4 Hz, 1 H) 7.4 (dt, *J*=8.6, 2.1 Hz, 2 H) 7.5 (s, 1 H) 7.6 (m, 1 H) 7.7 (dt, *J*=8.6, 1.9 Hz, 2 H) 8.2 (s, 1 H). ES-LCMS m/z = 593 (m + H^+).

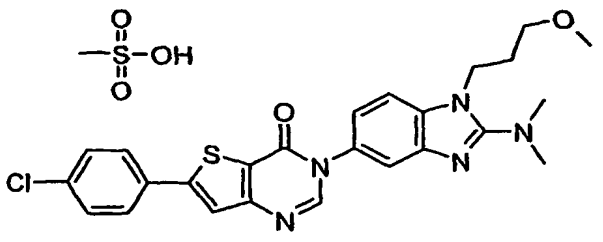
Example 55



6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[3-(methylamino)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

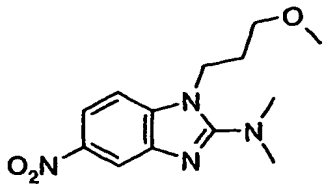
The compound obtained in Example 54, Step C (25 mg, 0.042 mmol) was dissolved in methanol and treated with methanesulfonic acid (11 μL, 0.17 mmol). The reaction was stirred overnight and purified by preparatory HPLC to provide the title compound as a white solid (15 mg). ^1H NMR (300 MHz, DMSO-d_6) δ 2.1 (m, 2 H) 2.6 (m, 3 H) 3.0 (t, *J*=7.7 Hz, 2 H) 3.2 (s, 6 H) 4.3 (t, *J*=6.9 Hz, 2 H) 7.4 (dd, *J*=8.0, 1.7 Hz, 1 H) 7.6 (dt, *J*=8.6, 1.9 Hz, 2 H) 7.6 (d, *J*=1.9 Hz, 1 H) 7.7 (d, *J*=8.6 Hz, 1 H) 7.9 (dt, *J*=8.8, 2.2 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). APCI-LCMS m/z = 593 (m + H^+).

Example 56



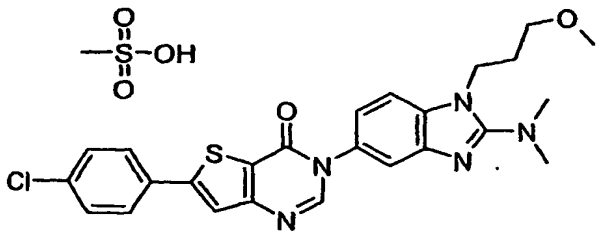
6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-methoxypropyl)-1*H*-

benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate



Step A: 1-(3-methoxypropyl)-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine

The intermediate obtained in Example 50, Step C (110 mg, 0.393 mmol) was dissolved in methanol, treated with sodium hydride (60%, 18 mg, 0.43 mmol), and stirred at 80 °C overnight. Starting material was not consumed by TLC. Potassium carbonate was then added and the reaction was stirred at 80 °C for one day. The reaction was filtered, concentrated, diluted with dichloromethane, and washed with water. The organic layer was dried, concentrated and the residue was purified using silica gel (0-100% ethyl acetate/hexanes) to provide the title compound as a yellow oil (75 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.1 (m, 2 H) 3.1 (s, 6 H) 3.3 (t, 3 H) 3.3 (t, *J*=5.5 Hz, 2 H) 3.5 (s, 1 H) 4.2 (m, 2 H) 7.2 (d, *J*=8.8 Hz, 1 H) 8.0 (dd, *J*=2.2 Hz, 1 H) 8.4 (d, *J*=2.1 Hz, 1 H). APCI-LCMS m/z = 279 (m + H$^+$).

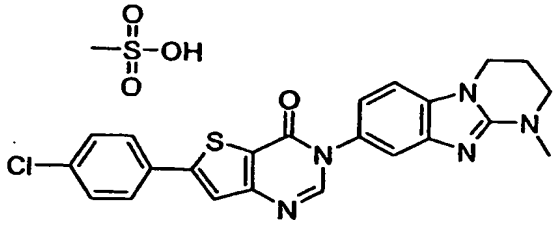


Step B: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-methoxypropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

The title compound was synthesized by substituting 1-(3-methoxypropyl)-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50, Step E. ^{1}H NMR (MsOH salt, 300 MHz, DMSO-d_6) δ 2.1 (m, 2 H) 2.3 (s, 3 H) 3.3 (s, 6 H) 3.4 (t, *J*=5.7 Hz, 2 H) 4.4 (t, *J*=6.6 Hz, 2 H)

7.5 (dd, *J*=8.6, 1.9 Hz, 1 H) 7.6 (dt, *J*=8.6, 1.9 Hz, 2 H) 7.7 (d, *J*=1.9 Hz, 1 H) 7.8 (d, *J*=8.6 Hz, 1 H) 8.0 (td, *J*=8.6, 1.9 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). ES-LCMS m/z = 494 ($m + H^+$).

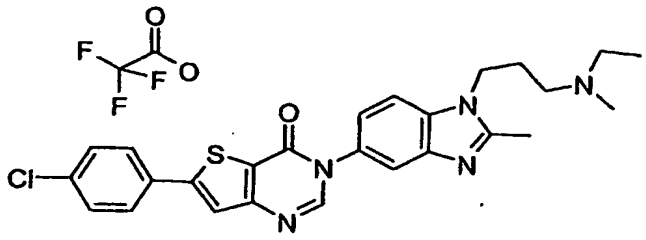
Example 57



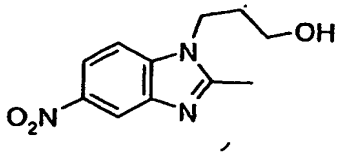
6-(4-chlorophenyl)-3-(1-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]benzimidazol-8-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

The title compound was synthesized by substituting 1-(3-chloropropyl)-*N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine (the intermediate produced in Example 50, step C) for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50, Step E. ^{1}H NMR (MsOH salt, 400 MHz, DMSO-d_6) δ 2.2 (m, 2 H) 2.3 (s, 3 H) 3.2 (s, 3 H) 3.6 (t, *J*=5.2 Hz, 2 H) 4.1 (t, *J*=6.0 Hz, 2 H) 7.5 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.6 (dt, *J*=8.6, 2.1 Hz, 2 H) 7.6 (d, *J*=8.6 Hz, 1 H) 7.7 (d, *J*=1.9 Hz, 1 H) 7.9 (dt, *J*=8.6, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS m/z = 448 ($m + H^+$).

Example 58

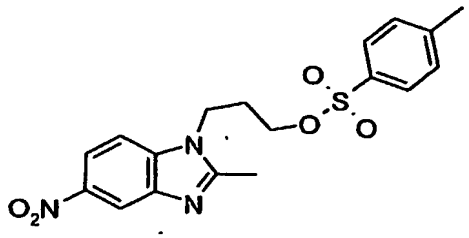


6-(4-chlorophenyl)-3-(1-{3-[ethyl(methyl)amino]propyl}-2-methyl-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 3-(2-Methyl-5-nitro-1*H*-benzimidazol-1-yl)propan-1-ol

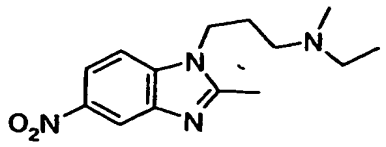
A solution of the intermediate obtained in Example 50, Step B (3.87 g, 18.3 mmol) in hot dimethyl acetamide was treated with acetyl chloride (5.18 mL, 73.2 mmol) and stirred for two hours. Concentrated aqueous hydrochloric acid (4 mL) was added and the reaction mixture was then heated to 100 °C and stirred for two hours. The reaction was cooled to room temperature, neutralized using 10 N sodium hydroxide, diluted with water, and extracted with ethyl acetate. The combined organics were dried and purified using silica gel (0-10% methanol/dichloromethane). Due to a small impurity, the resulting solid was recrystallized to afford a tan solid (1.74 g, 40% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.9 (m, 2 H) 2.6 (s, 3 H) 3.4 (q, *J*=4.8 Hz, 2 H) 4.3 (t, *J*=7.1 Hz, 2 H) 4.7 (t, *J*=4.9 Hz, 1 H) 7.7 (d, *J*=9.0 Hz, 1 H) 8.1 (dd, *J*=9.0, 2.2 Hz, 1 H) 8.4 (d, *J*=2.1 Hz, 1 H). ES-LCMS m/z = 236 (m + H$^+$).



Step B: 3-(2-methyl-5-nitro-1*H*-benzimidazol-1-yl)propyl 4-methylbenzenesulfonate

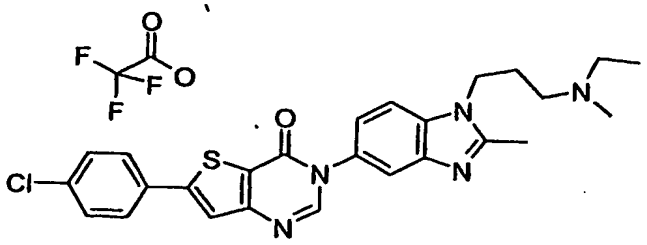
A solution of the intermediate obtained in Example 58, Step A (686 mg, 2.92 mmol) in warm tetrahydrofuran (45 mL) was treated tosyl chloride (1.22 g, 6.42 mmol) followed by sodium hydride (60% dispersion, 234 mg, 5.84 mmol) and stirred at 50 °C for three hours. The reaction was then concentrated, diluted with dichloromethane, and washed with water. The organic layer was dried and concentrated. The residue was recrystallized from dichloromethane and ethyl acetate and filtered to afford the title compound as a white solid

(1.06 g, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.0 (m, 2 H) 2.4 (s, 3 H) 2.5 (s, 3 H) 4.1 (t, *J*=6.0 Hz, 2 H) 4.3 (t, *J*=6.9 Hz, 2 H) 7.4 (d, *J*=7.9 Hz, 2 H) 7.6 (d, *J*=9.0 Hz, 1 H) 7.7 (dt, *J*=8.5, 2.0 Hz, 2 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.4 (d, *J*=2.2 Hz, 1 H). ES-LCMS m/z = 390 (m + H$^+$).



Step C: *N*-ethyl-*N*-methyl-3-(2-methyl-5-nitro-1*H*-benzimidazol-1-yl)-1-propanamine

The intermediate obtained in Example 58, Step B (124 mg, 0.318 mmol) was taken up in hot THF (4 mL), treated with N-ethylmethylamine (1 mL) and then potassium carbonate (88 mg, 0.64 mmol) was added. The reaction mixture was heated to 80 °C in a sealed tube and stirred overnight. After cooling, the reaction mixture was filtered, concentrated and purified on silica gel (0-10% 2.0 N NH_3 in $MeOH/CH_2Cl_2$) to afford the title compound as a white solid (71 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.9 (t, *J*=7.2 Hz, 3 H) 1.9 (m, 2 H) 2.1 (s, 3 H) 2.2 (m, 4 H) 2.6 (s, 3 H) 4.3 (t, *J*=7.1 Hz, 2 H) 7.7 (d, *J*=9.0 Hz, 1 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.4 (d, *J*=2.2 Hz, 1 H). ES-LCMS m/z = 277 (m + H$^+$).

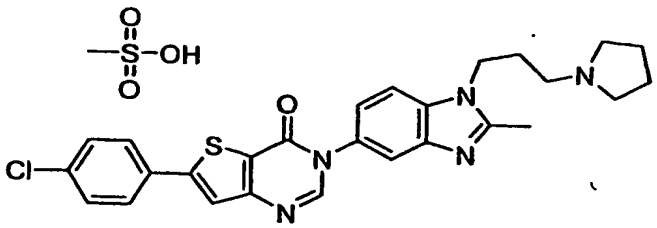


Step D: 6-(4-chlorophenyl)-3-(1-{3-[ethyl(methyl)amino]propyl}-2-methyl-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting the intermediate obtained in Example 58, Step C for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50,

Step E. ^{1}H NMR (TFA salt, 400 MHz, $CDCl_3$) δ 1.3 (t, *J*=7.2 Hz, 3 H) 2.4 (m, 2 H) 2.6 (s, 3 H) 2.8 (bs, 3 H) 2.8 (m, 2 H) 3.0 (m, 1 H) 3.2 (m, 2 H) 3.4 (m, 1 H) 4.5 (m, 2 H) 7.4 (dt, *J*=8.9, 2.2 Hz, 2 H) 7.5 (m, 2 H) 7.6 (dt, *J*=8.8, 2.4 Hz, 2 H) 7.9 (m, 2 H) 8.1 (s, 1 H) 12.0 (bs, 2 H). ES-LCMS m/z = 492 (m + H^+).

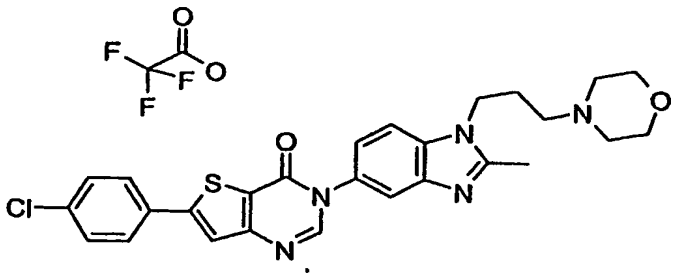
Example 59



6-(4-chlorophenyl)-3-{2-methyl-1-[3-(1-pyrrolidinyl)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

The title compound was synthesized by substituting pyrrolidine for N-ethylmethylamine and employing the techniques found in Example 58, Step C and Example 50, Step E. ^{1}H NMR (MsOH salt, 400 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 2.0 (m, 2 H) 2.2 (m, 2 H), 2.3 (s, 3 H) 2.8 (s, 3 H) 3.0 (m, 2 H) 3.3 (m, 2 H) 3.5 (m, 2 H) 7.6 (dt, *J*=8.8, 2.1 Hz, 2 H) 7.7 (d, *J*=8.6 Hz, 1 H) 7.9 (dt, *J*=8.8, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.1 (m, 2 H) 8.5 (s, 1 H) 9.6 (bs, 1 H). APCI-LCMS m/z = 505 (m + H^+).

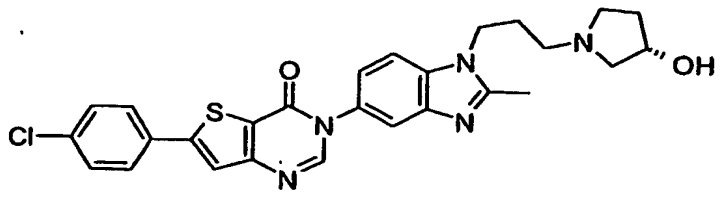
Example 60



6-(4-chlorophenyl)-3-{2-methyl-1-[3-(4-morpholinyl)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting morpholine for N-ethylmethylamine and employing the techniques found in Example 58, Step C and Example 50, Step E. ^{1}H NMR (TFA salt, 300 MHz, DMSO-d_6) δ 2.2 (m, 2 H) 2.7 (s, 3 H) 3.1 (m, 2 H) 3.3 (m, 2 H) 3.4 (m, 2 H) 3.6 (m, 2 H) 4.0 (m, 2 H) 4.4 (t, *J*=5.7 Hz, 2 H) 7.6 (m, 3 H) 7.9 (m, 4 H) 8.0 (s, 1 H) 8.5 (s, 1 H) 10.1 (bs, 1 H). ES-LCMS m/z = 520 (m + H$^+$).

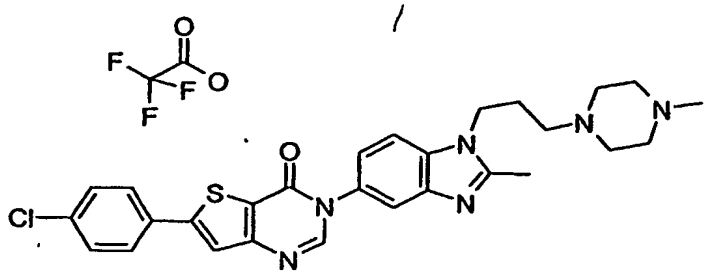
Example 61



6-(4-chlorophenyl)-3-(1-{3-[(3*S*)-3-hydroxy-1-pyrrolidinyl]propyl}-2-methyl-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was synthesized by substituting (3*S*)-3-pyrrolidinol for N-ethylmethylamine and employing the techniques found in Example 58, Step C and Example 50, Step E. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.8 (m, 1 H) 1.9 (m, 1 H) 2.1 (m, 2 H) 2.3 (m, 2 H) 2.5 (m, 3 H) 2.7 (m, 4 H) 2.9 (m, 1 H) 4.3 (t, *J*=6.9 Hz, 2 H) 4.4 (bs, 1 H) 7.3 (s, 1 H) 7.3 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.5 (m, 3 H) 7.6 (s, 1 H) 7.7 (m, 3 H) 8.2 (s, 1 H). ES-LCMS m/z = 533 (m + H$^+$).

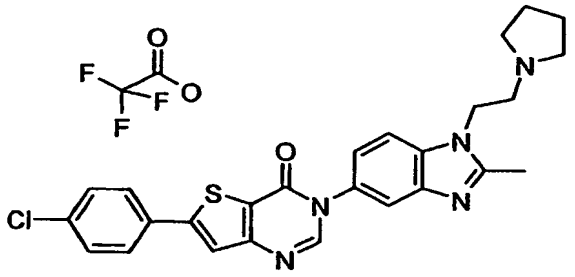
Example 62



6-(4-chlorophenyl)-3-{2-methyl-1-[3-(4-methyl-1-piperazinyl)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting 1-methylpiperazine for N-ethylmethylamine and employing the techniques found in Example 58, Step C and Example 50, Step E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (m, 2 H) 2.8 (m, 3 H) 2.9 (bs, 3 H) 3.6 (bs, 8 H) 4.6 (m, 2 H) 7.6 (dt, *J*=8.6, 1.9 Hz, 2 H) 7.7 (d, *J*=8.6 Hz, 1 H) 7.9 (dt, *J*=8.6, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.1 (d, *J*=1.4 Hz, 1 H) 8.2 (d, *J*=8.4 Hz, 1 H) 8.5 (s, 1 H). ES-LCMS m/z = 520 (m + H$^+$).

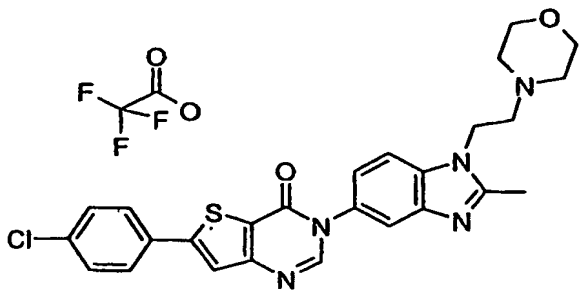
Example 63



6-(4-chlorophenyl)-3-{2-methyl-1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting [2-(1-pyrrolidinyl)ethyl]amine for 3-amino-1-propanol and employing the techniques found in Example 50, Steps A and B; Example 58, Step A; and Example 50, Step E, successively. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 1.9 (m, 2 H) 2.0 (m, 2 H) 2.7 (s, 3 H) 3.2 (m, 2 H) 3.6 (m, 4 H) 4.7 (t, *J*=4.0 Hz, 2 H) 7.5 (dd, *J*=8.8, 1.7 Hz, 1 H) 7.6 (dt, *J*=8.6, 2.1 Hz, 2 H) 7.9 (m, 4 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 10.2-(bs, 1 H). ES-LCMS m/z = 490 (m + H$^+$).

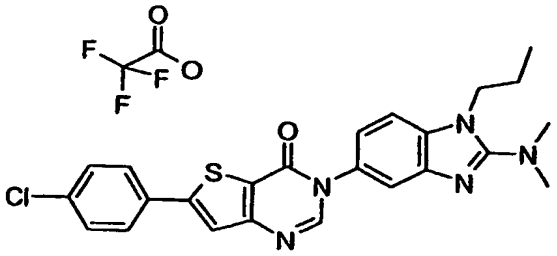
Example 64



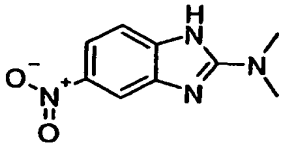
6-(4-chlorophenyl)-3-{2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting [2-(4-morpholinyl)ethyl]amine for [2-(1-pyrrolidinyl)ethyl]amine and employing the techniques found in Example 63. ^{1}H NMR (TFA salt, 300 MHz, DMSO-d_6) δ 2.7 (s, 3 H) 3.3 (m, 2 H) 3.5 (m, 2 H) 3.8 (m, 4 H) 4.5 (m, 2 H) 4.7 (t, *J*=6.9 Hz, 2 H) 7.6 (dd, *J*=8.6, 1.7 Hz, 1 H) 7.6 (dt, *J*=8.8, 1.9 Hz, 2 H) 7.9 (m, 2 H) 8.0 (dt, *J*=8.8, 2.2 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). ES-LCMS m/z = 506 (m + H$^+$).

Example 65

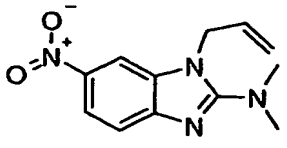
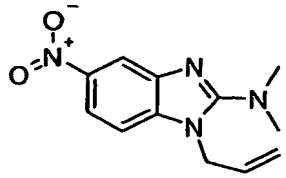


6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: *N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine

4-Nitro-1,2-benzenediamine (25 g, 163 mmol) and (dichloromethylene)dimethylammonium chloride ("phosgene iminium chloride") (26.5 g, 163 mmol) in 150 mL 1,2-dichloroethane were treated with triethylamine (45 mL, 326 mmol) and stirred overnight. The reaction was rinsed with water, and the organic layer was dried with magnesium sulfate, filtered and concentrated to afford the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.1 (s, 6 H) 7.2 (d, *J*=9.0 Hz, 1 H) 7.9 (s, 2 H) 11.8 (brs, 1 H).


and


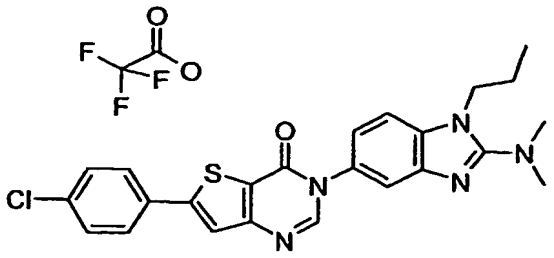
Step B: *N,N*-dimethyl-6-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine

and

N,N-dimethyl-5-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine

N,N-Dimethyl-5-nitro-1*H*-benzimidazol-2-amine (1.92 g, 9.3 mmol) in 10 mL dimethylformamide was treated with sodium hydride (560 mg, 14.0 mmol) and stirred for 10 minutes. To this was added allyl iodide (1.28 mL, 14 mL) and the reaction was stirred for 1 hour. The reaction was diluted with ethyl acetate and rinsed with brine three times. The organic layer was dried with magnesium sulfate, filtered and concentrated to afford a mixture of the desired products. The isomers were analyzed via SFC on a 4.6x250mm Berger Amino Column. A 10:90 Methanol:CO2 isocratic mobile phase with 3000 psi, 40 °C and a flow rate of 2mL/min was used to elute and resolve the isomers. The elution times for the isomers were ~3.3 and 4.0 minutes for *N,N*-dimethyl-6-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine and *N,N*-dimethyl-5-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine, respectively, the isomers being assigned by NMR nOe. The isomers seperated preparatively using 8% methanol in CO2 at a total flow rate of 90 g/min on BHK Labs Amino column, 30x250 mm 5u, pressure 145 bar, temp 40 °C, UV 250 nm, injection ~50 mg every 6 minutes. *N,N*-dimethyl-6-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine *N,N*-dimethyl-6-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.1 (s, 6 H) 4.8 (s, 2 H, nOe to 8.1) 5.0 (d, *J*=17.3 Hz, 1 H) 5.3 (d, *J*=10.2 Hz, 1 H) 6.1 (m, 1 H) 7.4 (d, *J*=8.6 Hz, 1 H) 8.0 (d, *J*=9.0 Hz, 1 H) 8.1 (s, 1 H).

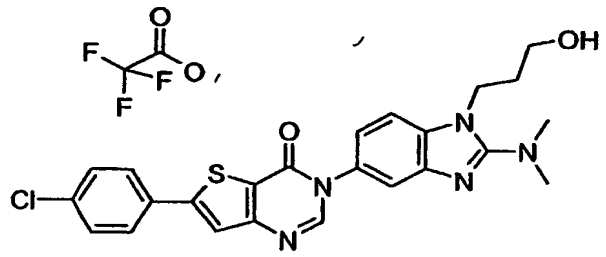
N,N-dimethyl-5-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.0 (s, 6 H) 4.8 (s, 2 H, nOe to 7.4) 5.0 (d, *J*=17.7 Hz, 1 H) 5.3 (d, *J*=9.6 Hz, 1 H) 6.1 (m, 1 H) 7.4 (d, *J*=8.7 Hz, 1 H) 8.0 (d, *J*=8.7 Hz, 1 H) 8.2 (s, 1 H).



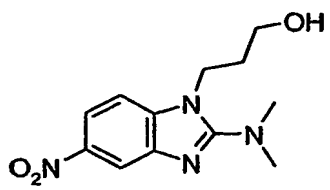
Step C: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting *N*,*N*-dimethyl-5-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50, Step E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 0.9 (t, *J*=7.2 Hz, 3 H) 1.8 (m, 2 H) 3.2 (s, 6 H) 4.2 (t, *J*=7.6 Hz, 2 H) 7.4 (d, *J*=8.3 Hz, 1 H) 7.6 (dt, *J*=8.6, 1.9 Hz, 2 H) 7.6 (d, *J*=1.9 Hz, 1 H) 7.8 (d, *J*=8.4 Hz, 1 H) 7.9 (dt, *J*=8.6, 1.9 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). APCI-LCMS m/z = 464 (m + H$^+$).

Example 66

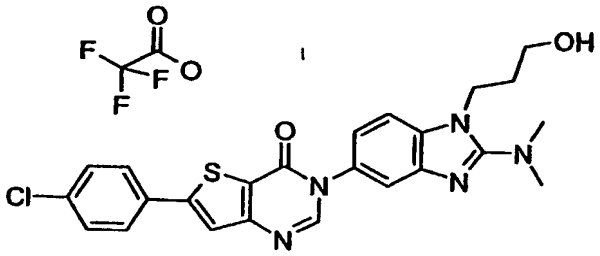


6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate (salt)



Step A: 3-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]-1-propanol

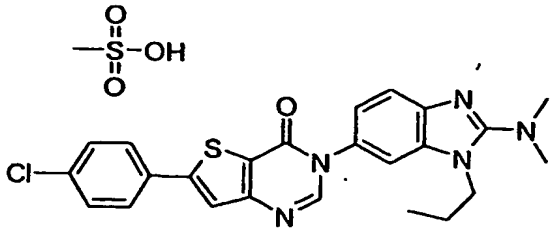
A solution of *N*,*N*-dimethyl-5-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine (the intermediate formed in Example 65, Step B; 100 mg, 0.406 mmol) in THF was cooled to 0 °C followed by dropwise addition of 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 2.4 mL, 1.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. Water (0.66 mL) was then added, followed by aqueous sodium hydroxide (10 N, 0.27 mL), and dropwise addition of hydrogen peroxide (30%, 0.66 mL). The reaction mixture was stirred for three hours, concentrated and purified using silica gel (0-10% methanol/dichloromethane) to provide the title compound as a yellow solid (62 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.1 (m, 2 H) 3.6 (m, 6 H) 4.3 (t, *J*=6.9 Hz, 2 H) 7.3 (d, *J*=9.5 Hz, 1 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.5 (d, *J*=2.1 Hz, 1 H). APCI-LCMS m/z = 265 (m + H$^+$).



Step B: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting 3-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]-1-propanol for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50, Step E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 2.0 (m, 2 H) 3.2 (s, 6 H) 3.5 (t, *J*=5.6 Hz, 2 H) 4.3 (m, 2 H) 7.4 (m, 1 H) 7.6 (dt, *J*=8.6, 1.7 Hz, 2 H) 7.6 (m, 1 H) 7.7 (m, 1 H) 7.9 (dt, *J*=8.6, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). APCI-LCMS m/z = 480 (m + H$^+$).

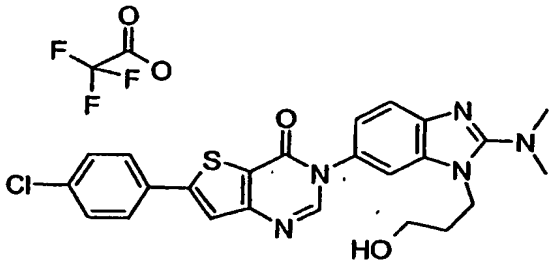
Example 67



6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-propyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

The title compound was synthesized by substituting *N*,*N*-dimethyl-6-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50, Step E. ^{1}H NMR (MsOH salt, 400 MHz, DMSO-d_6) δ 0.9 (t, *J*=7.4 Hz, 3 H) 1.8 (m, 2 H), 2.3 (s, 3H), 3.3 (s, 6 H) 4.2 (t, *J*=7.6 Hz, 2 H) 7.5 (dd, *J*=8.4, 1.4 Hz, 1 H) 7.6 (m, 3 H) 7.9 (dt, *J*=8.9, 2.7 Hz, 2 H) 8.0 (m, 1 H) 8.0 (s, 1 H) 8.5 (s, 1 H). APCI-LCMS m/z = 464 (m + H$^+$).

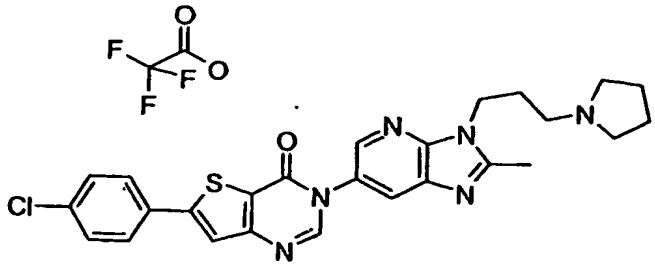
Example 68



6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(3-hydroxypropyl)-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate (salt)

The title compound was synthesized by substituting *N*,*N*-dimethyl-6-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine for *N*,*N*-dimethyl-5-nitro-1-(2-propen-1-yl)-1*H*-benzimidazol-2-amine (the intermediates produced in Example 65, Step A) and employing the techniques found in Example 66, Step A and Example 50, Step E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 2.0 (m, 2 H) 3.2 (s, 6 H) 3.5 (t, *J*=5.3 Hz, 2 H) 4.3 (t, *J*=7.1 Hz, 2 H) 7.4 (d, *J*=7.8 Hz, 1 H) 7.6 (d, *J*=8.3 Hz, 1 H) 7.6 (dt, *J*=8.8, 2.1 Hz, 2 H) 7.9 (m, 1 H) 7.9 (dt, *J*=8.6, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). APCI-LCMS m/z = 480 (m + H$^+$).

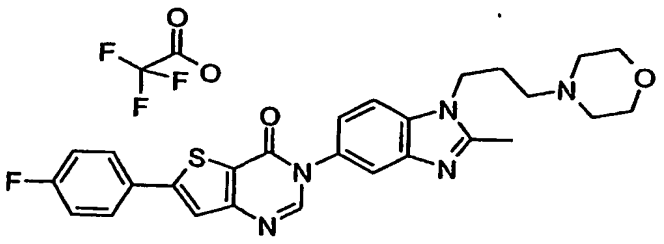
Example 69



6-(4-chlorophenyl)-3-{2-methyl-3-[3-(1-pyrrolidinyl)propyl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting 2-chloro-3,5-dinitropyridine for 2,4-dinitrofluorobenzene and [3-(1-pyrrolidinyl)propyl]amine for 3-amino-1-propanol and employing the techniques found in Example 50, Steps A, B, C, D, and E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 2.0 (m, 2 H) 2.2 (m, 2 H) 2.7 (s, 3 H) 3.0 (m, 2 H) 3.2 (m, 2 H) 3.6 (m, 2 H) 4.4 (t, *J*=6.7 Hz, 2 H) 7.6 (dt, *J*=8.8, 2.1 Hz, 2 H) 7.9 (dt, *J*=8.6, 2.1 Hz, 2 H) 8.0 (s, 1 H) 8.2 (d, *J*=2.2 Hz, 1 H) 8.5 (d, *J*=2.1 Hz, 1 H) 8.5 (s, 1 H) 9.5 (s, 1 H). APCI-LCMS m/z = 505 (m + H$^+$).

Example 70

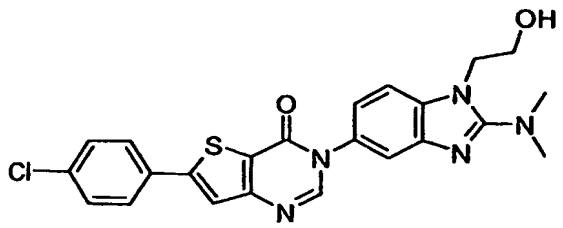


6-(4-fluorophenyl)-3-{2-methyl-1-[3-(4-morpholinyl)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

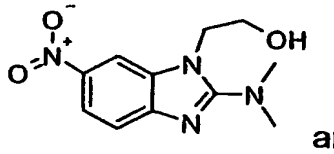
A solution of methyl 3-amino-5-(4-fluorophenyl)-2-thiophenecarboxylate (160 mg, 0.64 mmol) in N,N-dimethylformamide dimethyl acetal (2 mL) was heated to 105 °C, stirred for 90 minutes, and concentrated. The title compound was synthesized by substituting this crude material for methyl 3-amino-5-(4-

chlorophenyl)-2-thiophenecarboxylate and employing the techniques found in Example 60. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.2 (m, 2 H) 2.8 (s, 3 H) 3.1 (m, 2 H) 3.3 (m, 2 H) 3.4 (m, 2 H) 3.6 (m, 2 H) 4.0 (m, 2 H) 4.5 (t, *J*=7.2 Hz, 2 H) 7.4 (tt, *J*=8.8, 1.9 Hz, 2 H) 7.7 (dd, *J*=8.7, 1.8 Hz, 1 H) 8.0 (m, 5 H) 8.5 (s, 1 H). ES-LCMS m/z = 504 (m + H$^+$).

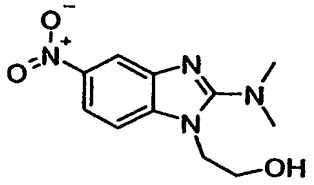
Example 71



6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



and



Step A: 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]ethanol

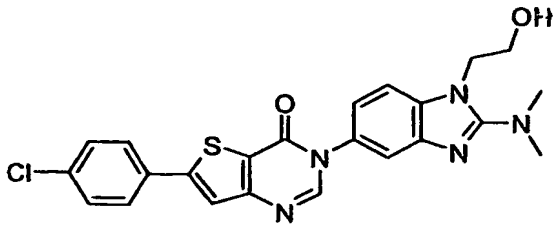
and

2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethanol

Following a procedure analogous to that for Example 65, Step B and substituting 2-bromo-1-ethanol, a mixture of the desired products was obtained. They were separated using 10% methanol in CO_2 at a total flow rate of 90 g/min, on a BHK Labs Amino column 30x250 mm 5u, pressure 140 bar, temp 30° C, UV 230 nm, injection ~65mg every 15 minutes. The faster eluting isomer was 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]ethanol, as determined by nOe. 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]ethanol, ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.1 (s, 6 H) 3.8 (m, 2 H) 4.3 (t, *J*=5.4 Hz, 2 H, nOe to 8.3) 5.1 (m, 1 H) 7.4 (d, *J*=8.7 Hz, 1 H) 8.0 (dd, *J*=8.9,

2.4 Hz, 1 H) 8.3 (d, *J*=2.2 Hz, 1 H).

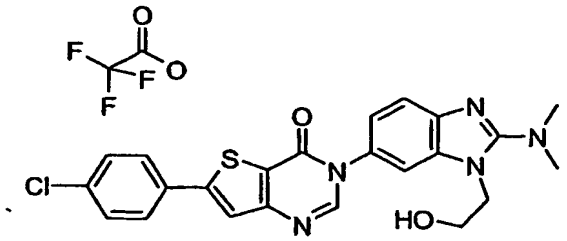
2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethanol, ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.0 (s, 6 H) 3.8 (q, *J*=5.5 Hz, 2 H) 4.2 (t, *J*=5.7 Hz, 2 H, nOe to 7.6) 5.1 (t, *J*=5.5 Hz, 1 H) 7.6 (d, *J*=8.7 Hz, 1 H) 8.0 (dd, *J*=8.9, 2.4 Hz, 1 H) 8.1 (d, *J*=2.0 Hz, 1 H).



Step B: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was synthesized by substituting 2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethanol for *N*,*N*-dimethyl-1-(3-morpholin-4-ylpropyl)-5-nitro-1*H*-benzimidazol-2-amine and employing the techniques found in Example 50, Step E. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 6 H) 3.8 (m, 2 H) 4.4 (m, 2 H) 7.5 (m, 1 H) 7.6 (m, 3 H) 7.8 (m, 1 H) 7.9 (m, 2 H) 8.0 (m, 1 H) 8.4 (s, 1 H). APCI-LCMS m/z = 466 (m + H$^+$).

Example 72

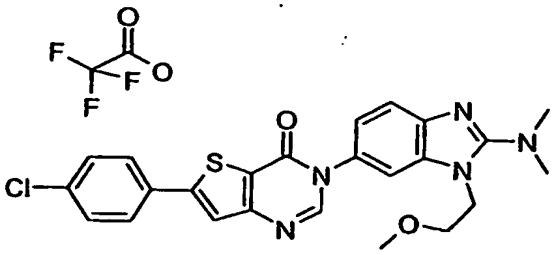


6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-(2-hydroxyethyl)-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

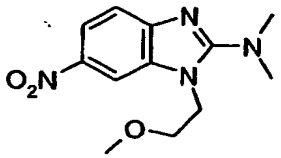
The title compound was synthesized by substituting 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]ethanol for 2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethanol and employing the techniques found in Example 50,

Step E. ^{1}H NMR (TFA salt, 400 MHz, DMSO-d_6) δ 2.3 (s, 3 H) 3.3 (s, 6 H) 3.8 (m, 2 H) 4.4 (m, 2 H) 7.5 (d, *J*=8.6 Hz, 1 H) 7.6 (m, 3 H) 7.9 (m, 3 H) 8.0 (s, 1 H) 8.5 (s, 1 H). APCI-LCMS m/z = 466 (m + H$^+$).

Example 73

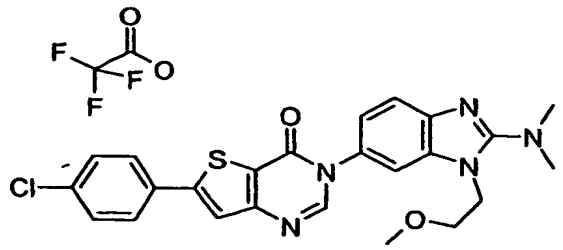


6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methyloxy)ethyl]-1*H*-benzimidazol-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: *N*,*N*-dimethyl-1-[2-(methyloxy)ethyl]-6-nitro-1*H*-benzimidazol-2-amine

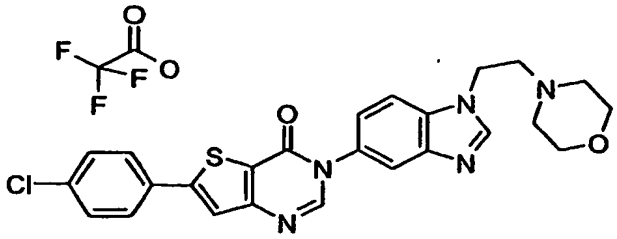
A solution of 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]ethanol (the intermediate obtained in Example 71, Step A, 104 mg) in THF was treated with methyl iodide (80 μL) cooled to 0 °C and treated with sodium hydride (35 mg, 60% suspension). The reaction was stirred for one hour, quenched with methanol, and purified by column chromatography to provide the title compound as a yellow solid (64 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.1 (s, 6 H) 3.4 (s, 3 H) 3.8 (t, *J*=5.5 Hz, 2 H) 4.3 (t, *J*=5.5 Hz, 2 H) 7.5 (d, *J*=8.8 Hz, 1 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.2 (d, *J*=2.2 Hz, 1 H). APCI-LCMS m/z = 265 (m + H$^+$).



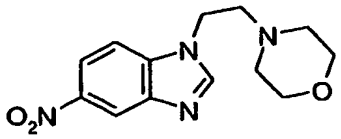
Step B: 6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(methyloxy)ethyl]-1*H*-benzimidazol-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting *N*,*N*-dimethyl-1-[2-(methyloxy)ethyl]-6-nitro-1*H*-benzimidazol-2-amine for 2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethanol and employing the techniques found in Example 50, Step E. ^{1}H NMR (TFA salt, 300 MHz, DMSO-d_6) δ 3.2 (s, 6 H) 3.8 (t, *J*=5.2 Hz, 2 H) 4.4 (t, *J*=5.2 Hz, 2 H) 7.5 (dd, *J*=8.7, 1.5 Hz, 1 H) 7.6 (m, 3 H) 7.9 (m, 1 H) 8.0 (dt, *J*=8.8, 2.2 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). APCI-LCMS m/z = 480 (m + H$^+$).

Example 74



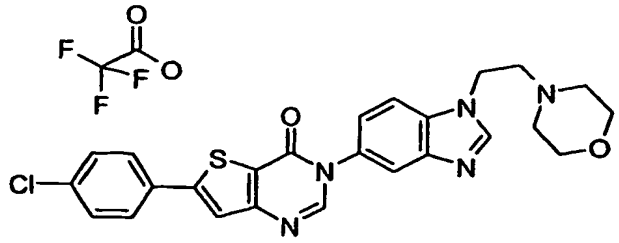
6-(4-chlorophenyl)-3-{1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 1-[2-(4-morpholinyl)ethyl]-5-nitro-1*H*-benzimidazole

A solution of *N*^{1}-[2-(4-morpholinyl)ethyl]-4-nitro-1,2-benzenediamine (the compound synthesized in Example 93, Step B) in DMF was treated with concentrated aqueous hydrochloric acid, heated to 100 °C and stirred for four hours. The reaction mixture was cooled and purified using silica gel to

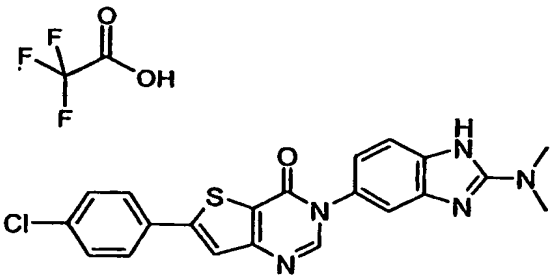
provide the title compound. ES-LCMS m/z = 277 (m + H$^+$).



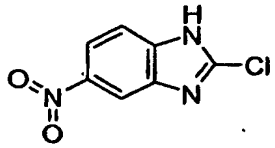
Step B: 6-(4-chlorophenyl)-3-{1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting 1-[2-(4-morpholinyl)ethyl]-5-nitro-1*H*-benzimidazole for 2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethanol and employing the techniques found in Example 50, Step E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.2 (m, 2 H) 3.6 (m, 6 H) 4.0 (m, 2 H) 4.7 (m, 2 H) 7.5 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.6 (dt, *J*=8.8, 2.1 Hz, 2 H) 7.9 (m, 4 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 8.5 (m, 1 H). ES-LCMS m/z = 492 (m + H$^+$).

Example 75



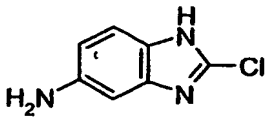
6-(4-chlorophenyl)-3-[2-(dimethylamino)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 2-chloro-5-nitro-1*H*-benzimidazole

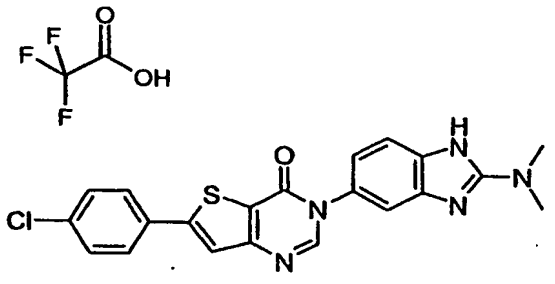
Conc. HNO_3 (8 mL) was added drop-wise to a mixture of 2-chloro-1*H*-

benzimidazole (4 g, 26.22 mmol) and conc. H_2SO_4 (25 mL) at 0 °C. The mixture stirred at 0 °C for 1 h. The reaction was charged with ice water (200 mL) and then extracted with EtOAc. The organics were dried over $MgSO_4$ (anhy.), filtered, and concentrated to dryness. The resulting crude was purified by silica gel chromatography (0-50% EtOAc/hexanes, 30min gradient; then 50% EtOAc/hexanes, 30 min). The resulting material was re-purified by silica gel chromatography (35% EtOAc/hexanes) to afford the title compound as a white solid (2.64g, 51% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.7 (d, J=8.8 Hz, 1 H) 8.1 (dd, J=8.9, 2.3 Hz, 1 H) 8.4 (d, J=2.1 Hz, 1 H). ES-LCMS m/z 197 (100), (M+H).



Step B: 2-chloro-1*H*-benzimidazol-5-amine

2-Chloro-5-nitro-1*H*-benzimidazole (Example 75, Step A; 2.15 g, 10.88 mmol) was added portion-wise to a solution of $Sn(II)Cl_2 \cdot 2H_2O$ (8.59 g, 38.08 mmol) in conc. HCl (30mL) at room temperature. The mixture stirred at room temperature for 15 min, then at 100 °C for 2 h. The reaction mixture was cooled to room temperature, poured into ice (100 g), and then made pH=8 with 10 N NaOH (aq). The mixture was charged with Rochelle's salt, then extracted with EtOAc. The organics were dried over $MgSO_4$ (anhy.), filtered, and concentrated to dryness to afford the title compound as a white solid (1.53 g, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.9 (s, 2 H) 6.5 (dd, J=8.4, 1.7 Hz, 1 H) 6.5 (s, 1 H) 12.5 (s, 1 H). ES-LCMS m/z 168 (100), (M+H).

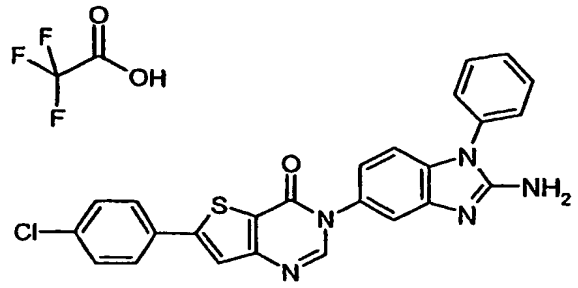


Step C: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

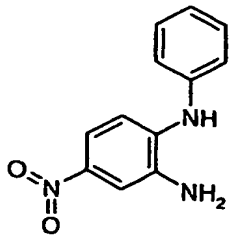
A mixture of 2-chloro-1*H*-benzimidazol-5-amine (Example 75, Step B; 50 mg, 0.3 mmol), dimethylamine (0.5 mL), and EtOH (3 mL) stirred at 100°C in a pressure tube for 25 h. Additional dimethylamine (3 mL) was added, and the mixture stirred at 160 °C in a pressure tube for 23 h. The reaction was cooled, and concentrated to dryness to afford the intermediate N^2,N^2-dimethyl-1*H*-benzimidazole-2,5-diamine ES-LCMS *m/z* 177 (M+H).

A mixture of methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (80 mg, 0.3 mmol) and N,N-dimethylformamide dimethyl acetal (3 mL) was stirred at 110 °C for 30 min. The reaction was then concentrated to dryness, and the resulting crude was charged with a solution of the above intermediate (N^2,N^2-dimethyl-1*H*-benzimidazole-2,5-diamine) in EtOH (5 mL). The mixture stirred at reflux for 19 h. The reaction was concentrated to dryness, taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as an off-white (39 mg, 24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.2 (m, 6 H) 7.4 (dd, *J*=8.3, 1.7 Hz, 1 H) 7.5 (d, *J*=8.4 Hz, 1 H) 7.6 (d, *J*=8.2 Hz, 2 H) 7.6 (d, *J*=1.8 Hz, 1 H) 7.9 (d, *J*=8.2 Hz, 2 H) 8.0 (d, *J*=0.7 Hz, 1 H) 8.4 (d, *J*=0.7 Hz, 1 H). APCI-LCMS *m/z* 422 (100), (M+H).

Example 76

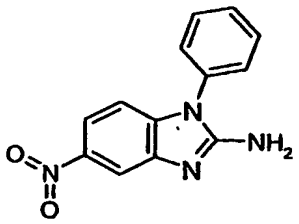


3-(2-amino-1-phenyl-1*H*-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



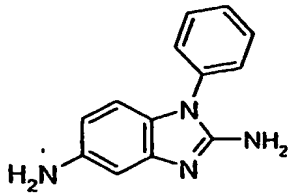
Step A: 4-nitro-N^1-phenyl-1,2-benzenediamine

A solution of $Na_2S_2O_4$ (20.15 g, 115.73 mmol) in H_2O (50 mL) was added to a solution of 2,4-dinitro-*N*-phenylaniline (10 g, 38.58 mmol) in EtOH (50 mL) and 2-propanol (100 mL) at reflux. The mixture stirred at reflux for 1 h. The mixture was concentrated, charged with H_2O, and extracted with CH_2Cl_2. The resulting crude mixture was purified by silica gel chromatography (25% EtOAc/hexanes) to afford the title compound as a red solid (3.8 g, 43% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.4 (s, 2 H) 7.0 (dd, *J*=7.3 Hz, 1 H) 7.0 (d, *J*=8.8 Hz, 1 H) 7.1 (dd, *J*=8.6, 1.0 Hz, 2 H) 7.3 (t, 2 H) 7.4 (dd, *J*=8.9, 2.7 Hz, 1 H) 7.6 (d, *J*=2.8 Hz, 1 H) 7.8 (s, 1 H). APCI-LCMS *m/z* 228 (100), (M-H).



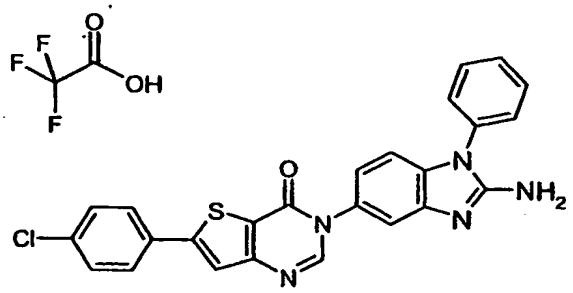
Step B: 5-nitro-1-phenyl-1*H*-benzimidazol-2-amine

3 M Cyanogen bromide in CH_2Cl_2 (6.6 mL, 16.95 mmol) was added to a solution of 4-nitro-N^1-phenyl-1,2-benzenediamine (Example 76, Step A; 2.59 g, 11.3 mmol) and CH_2Cl_2 (100 mL). The reaction stirred at room temperature for 24 h. The mixture was concentrated to dryness, and the resulting crude purified by silica gel chromatography (0-5% MeOH/CH_2Cl_2, 25 min gradient; then 5% MeOH/CH_2Cl_2, 10min) to afford the title compound as an orange solid (2.85 g, 99% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.1 (d, *J*=8.8 Hz, 1 H) 7.7 (m, 5 H) 8.1 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.2 (d, *J*=2.2 Hz, 1 H) 8.9 (s, 2 H). APCI-LCMS *m/z* 255 (100), (M+H).



Step C: 1-phenyl-1*H*-benzimidazole-2,5-diamine

A solution of $Na_2S_2O_4$ (616 mg, 3.54 mmol) in H_2O (2 mL) was added to a solution of 5-nitro-1-phenyl-1*H*-benzimidazol-2-amine (Example 76, Step B; 300 mg, 1.18 mmol) in EtOH (25 mL) at reflux. The mixture stirred at reflux for 1 h. The mixture was concentrated, and the resulting crude purified by silica gel chromatography (10% MeOH/CH_2Cl_2) to afford the title compound as a clear oil (80 mg, 30% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.2 (dd, *J*=8.2, 2.0 Hz, 1 H) 6.5 (m, *J*=2.0 Hz, 1 H) 6.6 (d, *J*=8.4 Hz, 1 H) 7.5 (m, 3 H) 7.6 (t, *J*=7.8 Hz, 2 H). APCI-LCMS *m/z* 225 (70), (M+H).

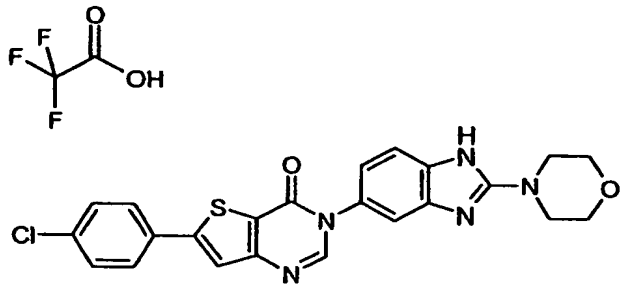


Step D: 3-(2-amino-1-phenyl-1*H*-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

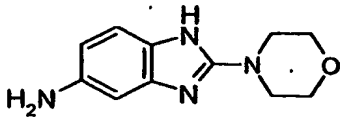
A mixture of methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (96 mg, 0.36 mmol) and N,N-dimethylformamide dimethyl acetal (3 mL) was stirred at 110 °C for 30 min. The reaction was then concentrated to dryness, and the resulting crude was charged with 1-phenyl-1*H*-benzimidazole-2,5-diamine (Example 76, Step C; 80 mg, 0.36 mmol) and EtOH (5 mL). The mixture was stirred at reflux 17 h. The reaction was concentrated to dryness, taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as an off-white solid (35

mg, 17% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.1 (d, *J*=8.4 Hz, 1 H) 7.3 (dd, *J*=8.7, 1.8 Hz, 1 H) 7.6 (d, *J*=8.4 Hz, 2 H) 7.7 (m, 6 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). APCI-LCMS *m/z* 470 (100), (M+H)

Example 77

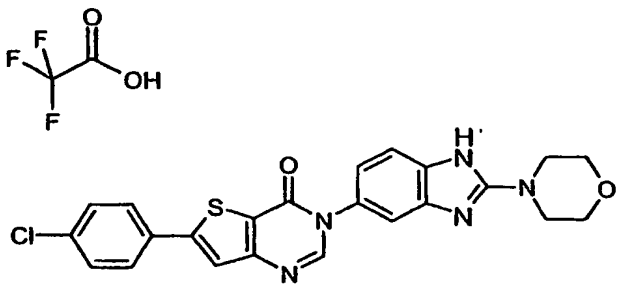


6-(4-chlorophenyl)-3-[2-(4-morpholinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 2-(4-morpholinyl)-1*H*-benzimidazol-5-amine

A mixture of 2-chloro-1*H*-benzimidazol-5-amine (Example 75, Step B; 60 mg, 0.36 mmol), morpholine (0.5 mL), and EtOH (5 mL) was stirred at refluxed for 64 h. The mixture was then stirred in a pressure tube at 130 °C for 2 h. The reaction was concentrated to dryness to afford the title compound as an orange solid (130 mg, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.5 (m, 1 H) 3.0 (m, 2 H) 3.3 (m, 2 H) 3.7 (m, 3 H) 6.3 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.5 (d, *J*=1.7 Hz, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). APCI-LCMS *m/z* 217 (100), (M-H).

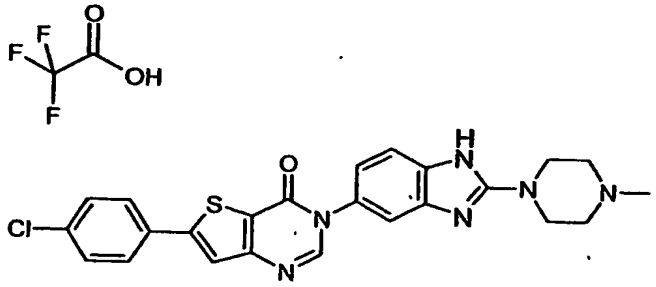


Step B: 6-(4-chlorophenyl)-3-[2-(4-morpholinyl)-1*H*-benzimidazol-5-

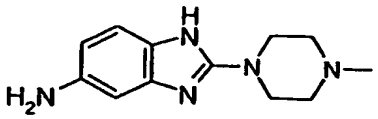
yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was prepared using a similar experimental procedure as in Example 76, Step D by substituting 2-(4-morpholinyl)-1*H*-benzimidazol-5-amine (Example 77, Step A; 74 mg, 0.34 mmol) for 1-phenyl-1*H*-benzimidazole-2,5-diamine to afford the title compound as an off-white solid (45 mg, 23% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.6 (m, 4 H) 3.8 (m, 4 H) 7.4 (dd, *J*=8.5, 1.7 Hz, 1 H) 7.5 (d, *J*=8.4 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.6 (s, 1 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 464 (100), (M+H).

Example 78



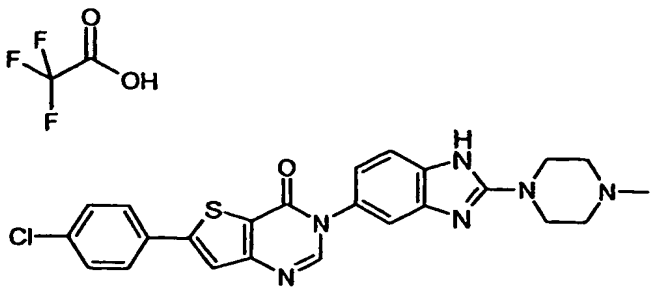
6-(4-chlorophenyl)-3-[2-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 2-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-5-amine

A mixture of 2-chloro-1*H*-benzimidazol-5-amine (Example 75, Step B; 100 mg, 0.6 mmol) and 1-methylpiperazine (2 mL) was stirred in a pressure tube at 130 °C for 2.5 h. The reaction was concentrated to dryness, and the resulting crude purified by silica gel chromatography (15% MeOH/CH_2Cl_2) to afford the title compound as a brown oil (113 mg, 84% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.2 (s, 3 H) 2.4 (m, 3 H) 3.0 (m, 3 H) 3.4 (m, 2 H) 6.2 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.4 (d, *J*=2.1 Hz, 1 H) 6.8 (d, *J*=8.1 Hz, 1 H). APCI-LCMS *m/z*

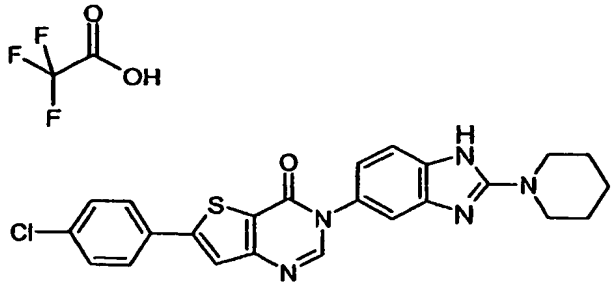
232 (80), (M+H).



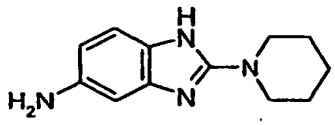
Step B: 6-(4-chlorophenyl)-3-[2-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was prepared using a similar experimental procedure as in Example 76, Step D by substituting 2-(4-methyl-1-piperazinyl)-1*H*-benzimidazol-5-amine (Example 78, Step A; 113 mg, 0.49 mmol) for 1-phenyl-1*H*-benzimidazole-2,5-diamine to afford the title compound as an off-white solid (24 mg, 8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.8 (s, 3 H) 3.2 (m, 4 H) 3.4 (m, 4 H) 7.2 (d, *J*=10.3 Hz, 1 H) 7.5 (d, *J*=8.3 Hz, 1 H) 7.5 (s, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). APCI-LCMS *m/z* 477 (100), (M+H).

Example 79

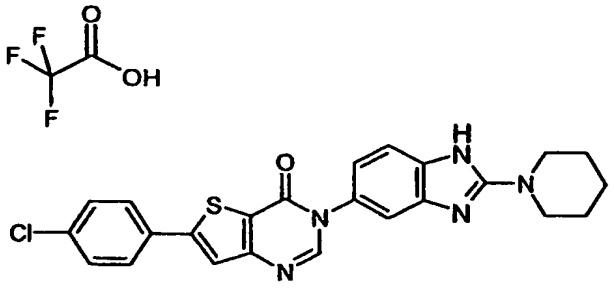


6-(4-chlorophenyl)-3-[2-(1-piperidinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 2-(1-piperidinyl)-1*H*-benzimidazol-5-amine

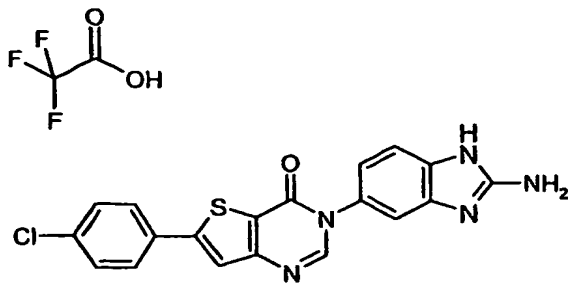
A mixture of 2-chloro-1*H*-benzimidazol-5-amine (Example 75, Step B; 100 mg, 0.6 mmol), piperidine (2 mL), and EtOH (2 mL) stirred in a pressure tube at 160 °C for 17 h. The reaction was concentrated to dryness, and the resulting crude purified by silica gel chromatography (0-10% MeOH/CH_2Cl_2, 20 min gradient; then 10% MeOH/CH_2Cl_2 for 20 min) to afford the title compound as a brown solid (111 mg, 86% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.6 (m, 4 H) 1.6 (m, 2 H) 3.0 (m, 2 H) 3.3 (s, 2 H) 6.3 (dd, *J*=8.1, 2.1 Hz, 1 H) 6.5 (d, *J*=2.1 Hz, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). APCI-LCMS *m/z* 217 (100), (M+H).



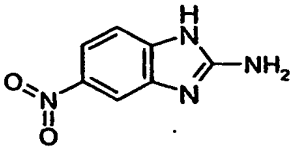
Step B: 6-(4-chlorophenyl)-3-[2-(1-piperidinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of 2-(1-piperidinyl)-1*H*-benzimidazol-5-amine (Example 79, Step A; 111 mg, 0.51 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 166 mg, 0.51 mmol) and EtOH (5 mL) stirred at reflux for 24 h. The reaction was concentrated to dryness, taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as a white solid (45 mg, 15% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.7 (m, 6 H) 3.6 (s, 4 H) 7.4 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.5 (d, *J*=8.4 Hz, 1 H) 7.6 (d, 2 H) 7.6 (d, *J*=1.9 Hz, 1 H) 7.9 (d, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 462 (100), (M+H).

Example 80

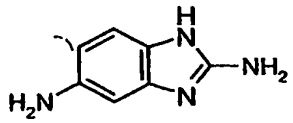


3-(2-amino-1*H*-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 5-nitro-1*H*-benzimidazol-2-amine

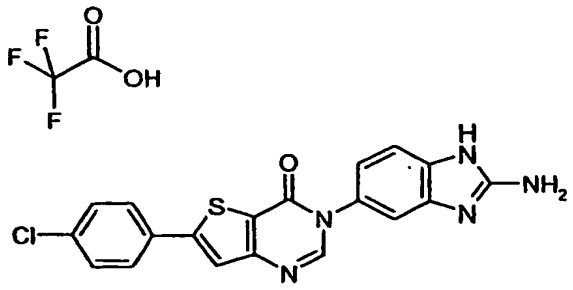
A mixture of (2-amino-4-nitrophenyl)amine (3 g, 19.6 mmol), 3 M cyanogen bromide in CH_2Cl_2 (6.53mL, 19.6mmol), MeOH (50mL) and H_2O (50mL) was stirred at room temperature for 18 h. The reaction was concentrated to dryness, and the resulting crude purified by silica gel chromatography (0-10% MeOH/CH_2Cl_2, 30 min gradient; then 10% MeOH/CH_2Cl_2 for 30 min) to afford the title compound as an orange solid (2.67 g, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.5 (d, *J*=8.6 Hz, 1 H) 8.1 (dd, 1 H) 8.1 (d, 1 H) 8.9 (s, 2 H). ES-LCMS *m/z* 179 (100), (M+H).



Step B: 1*H*-benzimidazole-2,5-diamine

A mixture of 5-nitro-1*H*-benzimidazol-2-amine (Example 80, Step A; 200 mg, 1.12 mmol), 10% Pd/C (20 mg), and EtOH (20 mL) stirred under an atmosphere of H_2 (1 atm) for 17.5 h. The reaction was filtered over Celite, and the filtrate concentrated to dryness to afford the title compound as a purple oil (200 mg, qualitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.3 (m,

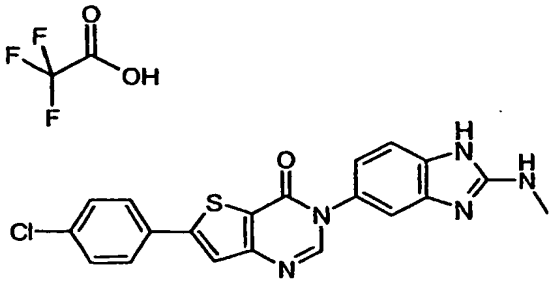
2 H) 6.4 (dd, *J*=8.4, 2.1 Hz, 1 H) 6.5 (d, *J*=1.7 Hz, 1 H) 7.0 (d, *J*=8.4 Hz, 1 H) 8.0 (s, 2 H). ES-LCMS *m/z* 149 (100), (M+H).



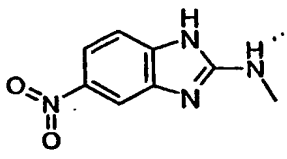
Step C: 3-(2-amino-1*H*-benzimidazol-5-yl)-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting 1*H*-benzimidazole-2,5-diamine (Example 80, Step B; 166 mg, 1.12 mmol) for 2-(1-piperidinyl)-1*H*-benzimidazol-5-amine and employing the techniques found in Example 79 Step B to afford the title compound as a yellow solid (155 mg, 27% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.4 (dd, *J*=8.4, 2.0 Hz, 1 H) 7.5 (d, *J*=8.5 Hz, 1 H) 7.6 (m, 3 H) 7.9 (d, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 8.7 (s, 2 H). APCI-LCMS *m/z* 394 (100), (M+H).

Example 81

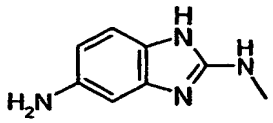


6-(4-chlorophenyl)-3-[2-(methylamino)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



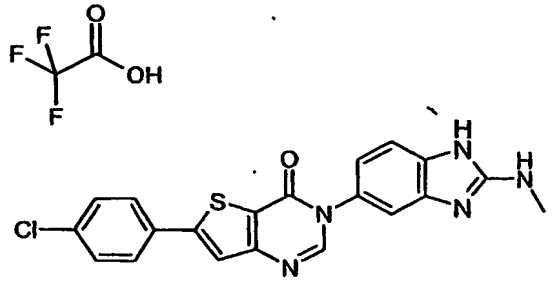
Step A: *N*-methyl-5-nitro-1*H*-benzimidazol-2-amine

A mixture of 2-chloro-5-nitro-1*H*-benzimidazole (Example 75, Step A; 100 mg, 0.51 mmol) and 2 M methylamine in MeOH (5 mL) stirred in a pressure tube at 160 °C for 24 h. The reaction was cooled, and concentrated to dryness to afford the title compound as an orange solid (162 mg, quantitative yield). The crude compound was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.9 (d, *J*=3.3 Hz, 3 H) 7.2 (m, *J*=8.4 Hz, 1 H) 7.3 (s, 1 H) 7.9 (d, *J*=8.4 Hz, 1 H) 7.9 (m, *J*=2.1 Hz, 1 H). ES-LCMS *m/z* 193 (100), (M+H).



Step B: N^2-methyl-1*H*-benzimidazole-2,5-diamine

A mixture of *N*-methyl-5-nitro-1*H*-benzimidazol-2-amine (Example 81, Step A; 162 mg, 0.54 mmol), 10% Pd/C (16 mg), and EtOH (25 mL) stirred under an atmosphere of H_2 (1 atm) for 4 h. The reaction was filtered over Celite, and the filtrate concentrated to dryness to afford the title compound as a brown oil (131 mg, 96% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.9 (s, 3 H) 6.3 (dd, *J*=8.3, 1.9 Hz, 1 H) 6.5 (d, *J*=1.9 Hz, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 163 (100), (M+H).

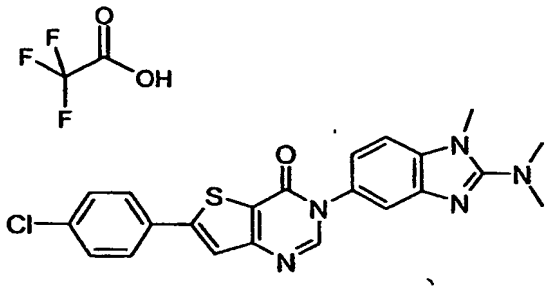


Step C: 6-(4-chlorophenyl)-3-[2-(methylamino)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

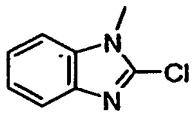
The title compound was synthesized by substituting N^2-methyl-1*H*-benzimidazole-2,5-diamine (Example 81, Step B; 131 mg, 0.81 mmol) for 2-

(1-piperidinyl)-1*H*-benzimidazol-5-amine and employing the techniques found in Example 79, Step B to afford the title compound as a tan solid (40 mg, 9% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.0 (d, *J*=4.8 Hz, 3 H) 7.4 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.5 (d, *J*=8.4 Hz, 1 H) 7.6 (m, *J*=8.4 Hz, 3 H) 7.9 (d, *J*=8.4 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 8.9 (s, 1 H). ES-LCMS *m/z* 408 (100), (M+H).

Example 82



6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



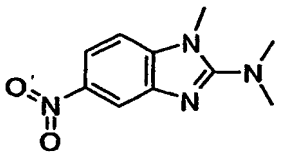
Step A: 2-chloro-1-methyl-1*H*-benzimidazole

Dimethylsulfate (5.5 mL) was added drop-wise to a solution of 2-chlorobenzimidazole (5 g, 32.77 mmol) and 10 N NaOH (aq) (7.5mL) in H_2O (57.5 mL) at 0 °C. The mixture stirred at 0 °C for 1 h and room temperature for 17 h. The resulting precipitate was filtered, washed with H_2O, azeotroped with toluene, and placed under a high vacuum to dry. The title compound was afforded as an off-white solid (4.04 g, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.8 (s, 3 H) 7.3 (m, 2 H) 7.6 (m, 2 H). APCI-LCMS *m/z* 167 (50), (M+H).

Step B: 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole and 2-chloro-1-methyl-6-

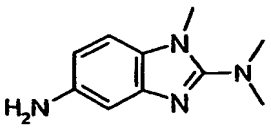
nitro-1*H*-benzimidazole

Conc. HNO_3 (8 mL) was added drop-wise to a mixture of 2-chloro-1-methyl-1*H*-benzimidazole (4.04 g, 24.25 mmol) and conc. H_2SO_4 (25 mL) at 0 °C. The mixture stirred at 0 °C for 1 h. The reaction was charged with ice water (200 mL), and then extracted with EtOAc. The organics were dried over $MgSO_4$ (anhy.), filtered, and concentrated to dryness. The resulting crude was purified by silica gel chromatography (0-50% EtOAc/hexanes, 30 min gradient; then 50% EtOAc/hexanes, 30 min) to afford 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole as a yellow solid (552 mg, 11% yield, Rf=0.625 50%EtOAc/hexanes): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.9 (s, 3 H) 7.8 (d, *J*=9.0 Hz, 1 H) 8.1 (d, *J*=8.9, 2.3 Hz, 1 H) 8.7 (m, *J*=2.1 Hz, 1 H), ES-LCMS *m/z* 211 (10), (M+H) and 2-chloro-1-methyl-6-nitro-1*H*-benzimidazole as a yellow solid (142mg, 3% yield, Rf=0.5 50%EtOAc/hexanes), ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.9 (s, 3 H) 7.8 (d, *J*=9.1 Hz, 1 H) 8.2 (dd, *J*=9.0, 2.2 Hz, 1 H) 8.5 (d, *J*=2.1 Hz, 1 H), ES-LCMS *m/z* 211 (100), (M+H).



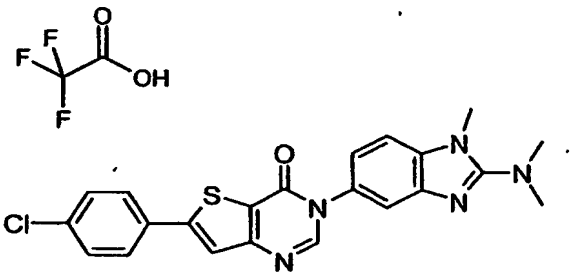
Step C: *N*,*N*,1-trimethyl-5-nitro-1*H*-benzimidazol-2-amine

A mixture of 2-chloro-1-methyl-5-nitro-1*H*-benzimidazole (Example 82, Step B; 140 mg, 0.66 mmol), 2 M dimethylamine in THF (1 mL), and EtOH (15 mL) stirred at 100 °C in a pressure tube for 4 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (10% MeOH/CH_2Cl_2) to afford the title compound as an orange solid (102 mg, 70% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.3 (s, 3 H) 3.7 (s, 6 H) 7.5 (s, 1 H) 8.0 (d, *J*=2.2 Hz, 1 H) 8.2 (d, *J*=2.2 Hz, 1 H). ES-LCMS *m/z* 221 (100), (M+H).



Step D: N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,5-diamine

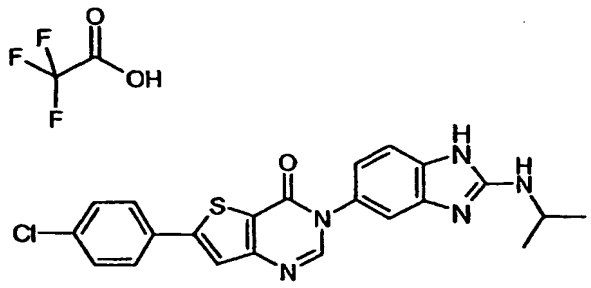
A mixture of *N*,*N*,1-trimethyl-5-nitro-1*H*-benzimidazol-2-amine (Example 82, Step C; 102 mg, 0.46 mmol), 10% Pd/C (10mg), and MeOH (10 mL) stirred under an atmosphere of H_2 (1 atm) for 1 h. The reaction was filtered over Celite, and the filtrate concentrated to dryness to afford the title compound as an orange oil (82 mg, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.8 (s, 6 H) 3.5 (s, 3 H) 4.5 (s, 7 H) 6.4 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.6 (d, *J*=1.9 Hz, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 191 (100), (M+H).



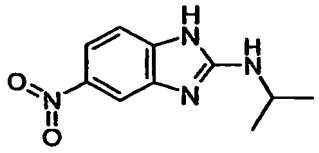
Step E: 6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,5-diamine (Example 82, Step D; 82 mg, 0.43 mmol) for 2-(1-piperidinyl)-1*H*-benzimidazol-5-amine and employing the techniques found in Example 79, Step B to afford the title compound as an off-white solid (16 mg, 7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.2 (s, 6 H) 3.8 (s, 3 H) 7.4 (d, *J*=8.8 Hz, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.6 (d, *J*=2.2 Hz, 1 H) 7.7 (d, *J*=8.4 Hz, 1 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 436 (100), (M+H).

Example 83

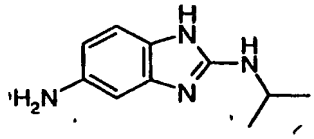


6-(4-chlorophenyl)-3-{2-[(1-methylethyl)amino]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: *N*-(1-methylethyl)-5-nitro-1*H*-benzimidazol-2-amine

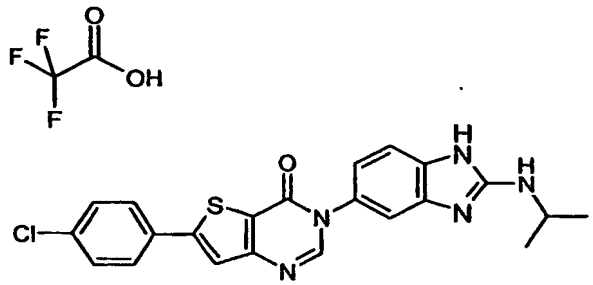
A mixture of 2-chloro-5-nitro-1*H*-benzimidazole (Example 75, Step A; 150 mg, 0.76 mmol), isopropylamine (647 μL, 7.6 mmol), and EtOH (5 mL) stirred in a pressure tube at 160 °C for 23 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (50-100% EtOAc/hexanes, 30 min gradient; then 100% EtOAc/hexanes, 15 min) to afford the title compound as a yellow solid (96 mg, 57% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.2 (s, 3 H) 1.2 (s, 3 H) 3.3 (s, 1 H) 3.9 (m, *J*=13.6, 7.0 Hz, 1 H) 7.2 (d, *J*=8.8 Hz, 1 H) 7.9 (d, *J*=8.2 Hz, 1 H) 7.9 (d, *J*=2.4 Hz, 1 H) 11.1 (d, 1 H). ES-LCMS *m/z* 221 (100), (M+H).



Step B: N^2-(1-methylethyl)-1*H*-benzimidazole-2,5-diamine

A mixture of *N*-(1-methylethyl)-5-nitro-1*H*-benzimidazol-2-amine (Example 83, Step A; 96 mg, 0.43 mmol), 10% Pd/C (10 mg), and MeOH (15 mL) stirred under an atmosphere of H_2 (1 atm) for 2 h. The reaction was filtered over celite, and the filtrate concentrated to dryness to afford the title compound as a brown solid (80 mg, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.1 (s, 3

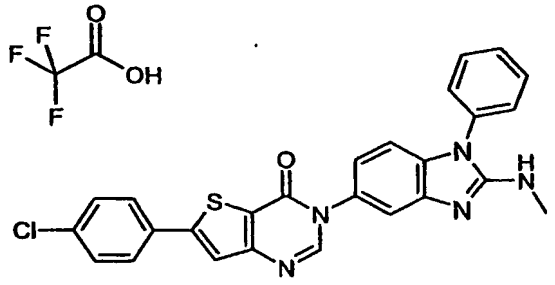
H) 1.1 (s, 3 H) 3.8 (m, 1 H) 4.3 (s, 1 H) 4.4 (s, 2 H) 6.0 (m, 2 H) 6.8 (dd, *J*=20.3, 8.2 Hz, 1 H) 10.1 (d, *J*=32.2 Hz, 1 H). ES-LCMS *m/z* 191 (100), (M+H).



Step C: 6-(4-chlorophenyl)-3-{2-[(1-methylethyl)amino]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting N^2-(1-methylethyl)-1*H*-benzimidazole-2,5-diamine (Example 83, Step B; 80 mg, 0.42 mmol) for 2-(1-piperidinyl)-1*H*-benzimidazol-5-amine and employing the techniques found in Example 79, Step B to afford the title compound as an off-white solid (16 mg, 7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.3 (s, 3 H) 1.3 (s, 3 H) 3.9 (m, 1 H) 7.4 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.5 (d, *J*=8.4 Hz, 1 H) 7.6 (m, 3 H) 7.9 (m, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.1 (s, 1 H). ES-LCMS *m/z* 436 (100), (M+H).

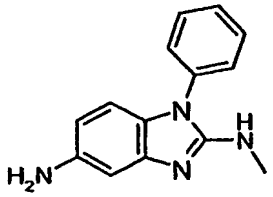
Example 84



6-(4-chlorophenyl)-3-[2-(methylamino)-1-phenyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

Step A: *N*-methyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine and *N*,*N*-dimethyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine

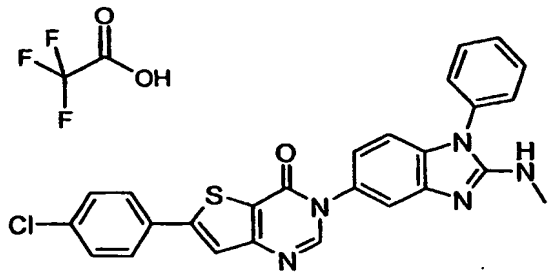
NaH (71 mg, 2.96 mmol) was added to a solution of 5-nitro-1-phenyl-1*H*-benzimidazol-2-amine (Example 76, Step B; 500 mg, 1.97 mmol) in DMF (15 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, then iodomethane (184 μL, 2.96 mmol) was added at 0 °C. The mixture was stirred at room temperature for 16 h. The reaction was charged with H_2O, and extracted with EtOAc. The organics were dried over $MgSO_4$ (anhy), filtered, and concentrated to dryness. The resulting crude was purified by silica gel chromatography (0-80% EtOAc/hexanes, 90 min gradient) to afford *N*-methyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine as a yellow solid (107 mg, 20% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.9 (d, *J*=4.6 Hz, 3 H) 6.7 (m, *J*=4.5, 4.5, 4.5 Hz, 1 H) 6.9 (d, *J*=8.8 Hz, 1 H) 7.5 (m, 2 H) 7.6 (m, 1 H) 7.6 (m, 2 H) 7.8 (dd, *J*=8.7, 2.3 Hz, 1 H) 8.1 (d, *J*=2.2 Hz, 1 H), APCI-LCMS *m/z* 269 (100), (M+H) and *N*,*N*-dimethyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine as a yellow solid (79 mg, 14% yield). ^{1}H NMiR (400 MHz, DMSO-d_6) δ 2.8 (s, 6 H) 7.0 (d, *J*=8.8 Hz, 1 H) 7.6 (m, 3 H) 7.6 (m, 2 H) 7.9 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.1 (d, *J*=2.2 Hz, 1 H), APCI-LCMS *m/z* 283 (100), (M+H).



Step B: N^2-methyl-1-phenyl-1*H*-benzimidazole-2,5-diamine

A mixture of *N*-methyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine (Example 84, Step A; 107 mg, 0.40 mmol), 10% Pd/C (10 mg), and EtOH (20 mL)

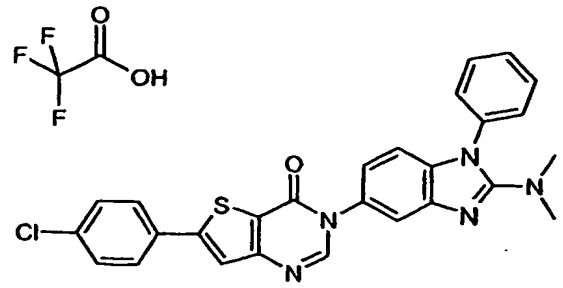
stirred under an atmosphere of H_2 (1 atm) for 2 h. The reaction was filtered over celite, and the filtrate concentrated to dryness to afford the title compound as a tan residue (94 mg, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.8 (d, *J*=4.7 Hz, 3 H) 4.5 (s, 2 H) 6.0 (d, *J*=4.3 Hz, 1 H) 6.2 (dd, *J*=8.2, 2.2 Hz, 1 H) 6.5 (m, 2 H) 7.4 (m, 3 H) 7.6 (m, 2 H). ES-LCMS *m/z* 239 (100), (M+H).



Step C: 6-(4-chlorophenyl)-3-[2-(methylamino)-1-phenyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of N^2-methyl-1-phenyl-1*H*-benzimidazole-2,5-diamine (Example 84, Step B; 90 mg, 0.38 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 75, Step D; 122 mg, 0.38 mmol) and phenol (2 mL) stirred at reflux for 15 min. The reaction was charged with additional methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 75, Step D; 61 mg, 0.19 mmol) and stirred at reflux for 15 min. The reaction was taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as a white solid (55 mg, 24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.0 (d, *J*=4.8 Hz, 3 H) 7.1 (d, *J*=8.4 Hz, 1 H) 7.3 (d, *J*=9.0 Hz, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.7 (m, 6 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 484 (100), (M+H).

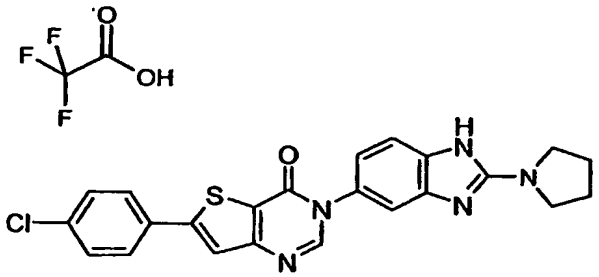
Example 85



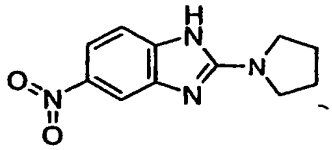
6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-phenyl-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting *N*,*N*-dimethyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine (Example 84, Step A; 79 mg, 0.28 mmol) for *N*-methyl-5-nitro-1-phenyl-1*H*-benzimidazol-2-amine and employing the techniques found in Example 84, Steps B and C to afford an off-white solid (21 mg, 13% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.9 (s, 6 H) 7.0 (d, *J*=8.6 Hz, 1 H) 7.3 (m, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.7 (m, 6 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 498 (100), (M+).

Example 86



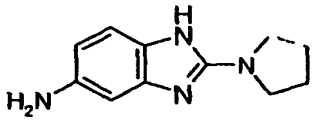
6-(4-chlorophenyl)-3-[2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 5-nitro-2-(1-pyrrolidinyl)-1*H*-benzimidazole

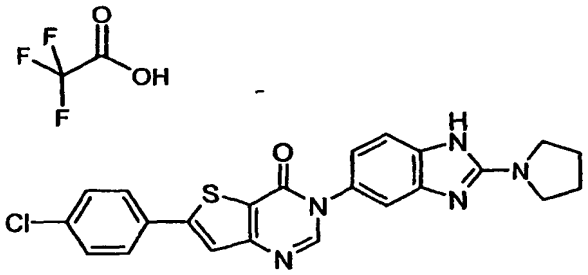
A mixture of 2-chloro-5-nitro-1*H*-benzimidazole (Example 75, Step A; 100 mg,

0.6 mmol), pyrrolidine (2 mL), and EtOH (10 mL) stirred in a pressure tube at 160 °C for 18 h. The reaction was and concentrated to dryness to afford the title compound as a brown oil (213 mg, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.0 (m, 4 H) 3.5 (m, 4 H) 7.2 (dd, *J*=8.6, 0.5 Hz, 1 H) 7.9 (m, 2 H). APCI-LCMS *m/z* 233 (100), (M+H).



Step B: 2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-amine

A mixture of 5-nitro-2-(1-pyrrolidinyl)-1*H*-benzimidazole (Example 86, Step A; 139 mg, 0.6 mmol), 10% Pd/C (10 mg), and MeOH (10 mL) stirred under an atmosphere of H_2 (1 atm) for 1 h. The reaction was filtered over celite, and the filtrate concentrated to dryness to afford the title compound as a tan solid (186 mg, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.9 (m, 4 H) 3.4 (m, 4 H) 6.2 (dd, *J*=8.2, 2.2 Hz, 1 H) 6.4 (d, *J*=2.1 Hz, 1 H) 6.8 (d, *J*=8.3 Hz, 1 H). APCI-LCMS *m/z* 203 (100), (M+H).

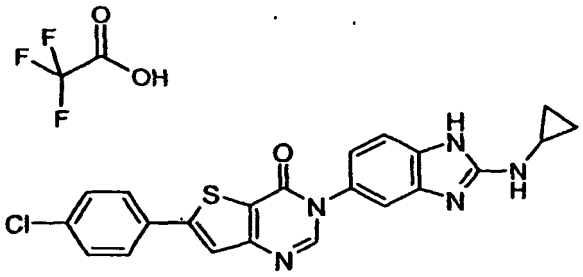


Step C: 6-(4-chlorophenyl)-3-[2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of 2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-amine (Example 86, Step B; 121 mg, 0.6 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 86 mg, 0.27 mmol), and phenol (2 mL) stirred at 200 °C for 30min. The mixture was cooled to room temperature, then partitioned between EtOAc and 1N NaOH (aq). The organics were concentrated to dryness, and the resulting crude was taken up in DMSO, and purified by C18 preparative HPLC (1-99%

CH_3CN/H_2O 5 min gradient) to afford the title compound as an off-white solid (50 mg, 15% yield). H NMR (400 MHz, DMSO-d_6) δ 2.1 (m, 4 H) 3.6 (m, 4 H) 7.4 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.5 (d, *J*=8.3 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.6 (d, *J*=1.9 Hz, 1 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 13.0 (s, 1 H). ES-LCMS *m/z* 448 (100), (M+H).

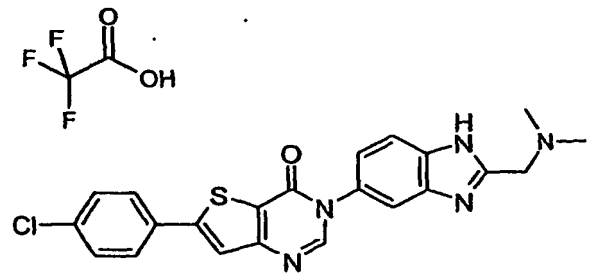
Example 87



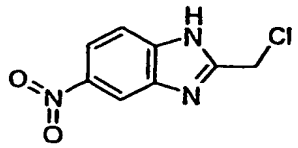
6-(4-chlorophenyl)-3-[2-(cyclopropylamino)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting cyclopropylamine (1 mL) for pyrrolidine and employing the techniques found in Example 86, Steps A, B, and C to afford an off-white solid (16 mg, 11% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.7 (m, 2 H) 0.9 (m, 2 H) 2.8 (s, 1 H) 7.4 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.5 (d, *J*=8.1 Hz, 1 H) 7.6 (m, 3 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.4 (s, 1 H) 12.9 (s, 1 H). ES-LCMS *m/z* 434 (100), (M+H).

Example 88

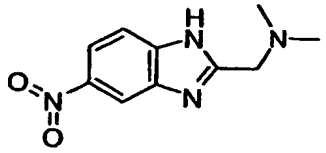


6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



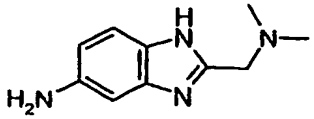
Step A: 2-(chloromethyl)-5-nitro-1*H*-benzimidazole

A mixture of 2-(chloromethyl)-1*H*-benzimidazole (1 g, 6 mmol), conc. HNO_3 (2 mL), and conc. H_2SO_4 (6 mL) stirred at 0 °C for 30 min. The reaction was charged with ice water (200 mL), and then extracted with EtOAc. The organics were dried over $MgSO_4$ (anhy.), filtered, and concentrated to dryness to afford the title compound as an orange solid (940 mg, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.0 (s, 2 H) 7.7 (d, *J*=9.3 Hz, 1 H) 8.1 (dd, *J*=9.0, 2.2 Hz, 1 H) 8.5 (d, *J*=2.4 Hz, 1 H). APCI-LCMS *m/z* 210 (100), (M-H).



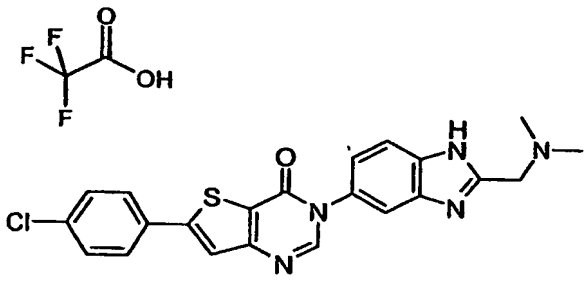
Step B: *N*,*N*-dimethyl-1-(5-nitro-1*H*-benzimidazol-2-yl)methanamine

A mixture of 2-(chloromethyl)-5-nitro-1*H*-benzimidazole (Example 88, Step A; 940 mg, 4.44 mmol), 2 M dimethylamine in MeOH (10 mL), and MeOH (20 mL) stirred at 100 °C in a pressure tube for 17 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-10% MeOH/CH_2Cl_2, 30 min gradient; then 10% MeOH/CH_2Cl_2, 30 min) to afford the title compound as an orange solid (350 mg, 36% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.2 (s, 6 H) 3.7 (s, 2 H) 7.6 (s, 1 H) 8.1 (d, *J*=7.8 Hz, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 221 (100), (M+H).



Step C: 2-[(dimethylamino)methyl]-1*H*-benzimidazol-5-amine

N,*N*-Dimethyl-1-(5-nitro-1*H*-benzimidazol-2-yl)methanamine (Example 88, Step B; 350 mg, 1.59 mmol) was added portion-wise to a solution of $Sn(II)Cl_2 \cdot 2H_2O$ (1.26 g, 5.56 mmol) in conc. HCl (5 mL) at room temperature. The mixture stirred at room temperature for 15 min, then at 100 °C for 2h. The reaction mixture was cooled to room temperature, poured into ice, made pH=8 with 10 N NaOH (aq), then concentrated to dryness. The crude residue was stirred in $MeOH/CH_2Cl_2$, then hot filtered. The filtrate was concentrated to dryness, and the crude reside was purified by silica gel chromatography (0-15% 2M ammonia in $MeOH/CH_2Cl_2$, 30 min gradient; then 15% 2 M ammonia in $MeOH/CH_2Cl_2$, 30 min) to afford the title compound as a tan solid (160 mg, 53% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 2.2 (s, 6 H) 3.5 (s, 2 H) 6.4 (dd, *J*=8.4, 2.2 Hz, 1 H) 6.6 (s, 1 H) 7.1 (d, *J*=8.4 Hz, 1 H). ES-LCMS *m/z* 191 (30), (M+H).

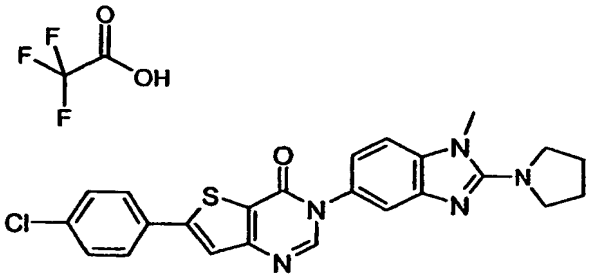


Step D: 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

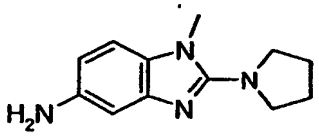
A mixture of 2-[(dimethylamino)methyl]-1*H*-benzimidazol-5-amine (Example 88, Step C; 50 mg, 0.27 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 75, Step D; 271 mg, 0.84 mmol), and phenol (2 g) stirred at 200 °C for 30 min. The mixture was cooled to room temperature, charged with 1 N NaOH (aq) (40 mL), then extracted with CH_2Cl_2. The organics were dried over $MgSO_4$ (anhy.), filtered, and the filtrate concentrated to dryness. The resulting crude was stirred in MeOH at reflux until homogeneous, and upon cooling a tan precipitate formed. This precipitate was filtered, taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to

afford the title compound as a white solid (25 mg, 5% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.9 (s, 6 H) 4.6 (s, 2 H) 7.4 (dd, *J*=8.5, 2.0 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.8 (d, *J*=8.4 Hz, 1 H) 7.9 (d, *J*=1.9 Hz, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). ES-LCMS *m/z* 436 (100), (M+H).

Example 89

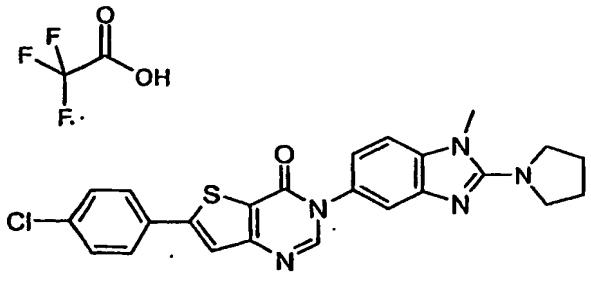


6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: 1-methyl-2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-amine

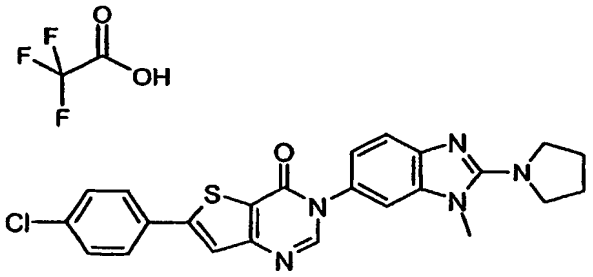
A mixture of 2-chloro-1-methyl-1*H*-benzimidazol-5-amine (Example 11, Step C; 200 mg, 1.1 mmol), pyrrolidine (2 mL), and EtOH (10 mL) stirred in a pressure tube at 160 °C for 21.5 h. The reaction was and concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-7.5% MeOH/CH_2Cl_2, 1h gradient) to afford the title compound as a pink solid (161 mg, 68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.9 (m, 4 H) 3.5 (m, 4 H) 3.5 (s, 3 H) 6.3 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.5 (d, *J*=2.2 Hz, 1 H) 6.9 (d, *J*=8.4 Hz, 1 H). ES-LCMS *m/z* 217 (100), (M+H).



Step B: 6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of 1-methyl-2-(1-pyrrolidinyl)-1*H*-benzimidazol-5-amine (Example 89, Step A; 161 mg, 0.75 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 241 mg, 0.75 mmol), and phenol (1 g) stirred at 200 °C for 30 min. The mixture was cooled to room temperature, charged with 1 N NaOH (aq) (15 mL), then extracted with CH_2Cl_2. The organics were dried over $MgSO_4$ (anhy.), filtered, and the filtrate concentrated to dryness. The resulting crude was charged with DMSO (2 mL) and EtOH (5 mL). The resulting yellow precipitate was filtered, washed with EtOH, then taken up in DMSO (3 mL) and a drop of TFA, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5min gradient) to afford the title compound as a white solid (179 mg, 41% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.0 (m, 4 H) 3.8 (t, *J*=6.5 Hz, 4 H) 3.9 (s, 3 H) 7.5 (dd, *J*=8.6, 1.9 Hz, 1 H) 7.6 (m, 2 H) 7.6 (d, *J*=1.9 Hz, 1 H) 7.7 (d, *J*=8.6 Hz, 1 H) 7.9 (m, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 462 (100), (M+H).

Example 90

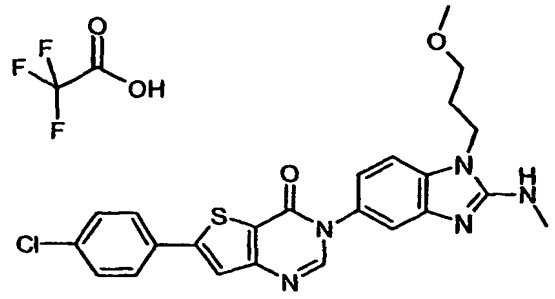


6-(4-chlorophenyl)-3-[1-methyl-2-(1-pyrrolidinyl)-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

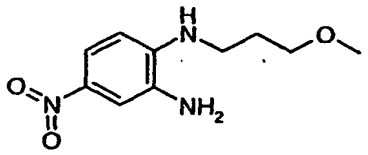
The title compound was synthesized by substituting 2-chloro-1-methyl-1*H*-benzimidazol-6-amine (Example 85, Step C; 200 mg, 1.1 mmol) for 2-chloro-1-methyl-1*H*-benzimidazol-5-amine and employing the techniques found in

Example 89, Steps A and B to afford a white solid (295 mg, 51% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.9 (m, 4 H) 3.4 (t, *J*=6.7 Hz, 4 H) 3.5 (s, 3 H) 4.7 (s, 2 H) 6.3 (dd, *J*=8.1, 2.3 Hz, 1 H) 6.4 (d, *J*=2.0 Hz, 1 H) 6.9 (d, *J*=8.4 Hz, 1 H). ES-LCMS *m/z* 217 (100), (M+H).

Example 91

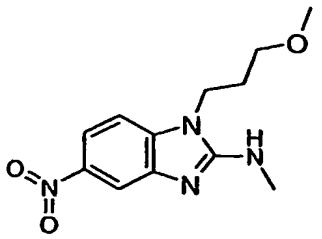


6-(4-chlorophenyl)-3-{2-(methylamino)-1-[3-(methyloxy)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



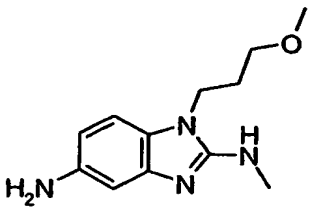
Step A: N^1-[3-(methyloxy)propyl]-4-nitro-1,2-benzenediamine

A mixture of 2-fluoro-5-nitroaniline (1 g, 6.41 mmol), [3-(methyloxy)propyl]amine (571 mg, 6.41 mmol), and EtOH (10 mL) stirred at reflux for 1 h, then in a pressure tube at 160 °C for 20 h. The reaction was charged with additional [3-(methyloxy)propyl]amine (2.5 mL) and then stirred in a pressure tube at 160 °C for 24 h. The mixture was concentrated, and the resulting crude purified by silica gel chromatography (CH_2Cl_2) to afford the title compound as an orange solid (350 mg, 24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 3.2 (m, 5 H) 3.4 (t, *J*=6.1 Hz, 2 H) 5.1 (s, 2 H) 5.9 (t, *J*=5.2 Hz, 1 H) 6.4 (d, *J*=8.8 Hz, 1 H) 7.4 (d, *J*=2.7 Hz, 1 H) 7.5 (dd, *J*=8.8, 2.7 Hz, 1 H). ES-LCMS *m/z* 226 (100), (M+H).



Step B: *N*-methyl-1-[3-(methyloxy)propyl]-5-nitro-1*H*-benzimidazol-2-amine

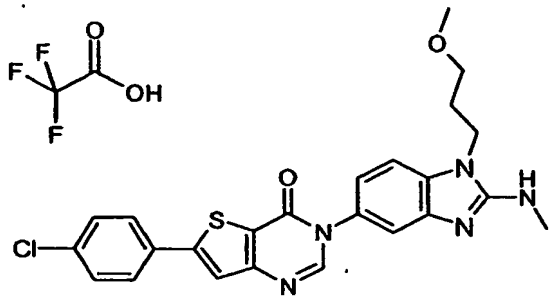
A mixture of N^1-[3-(methyloxy)propyl]-4-nitro-1,2-benzenediamine (Example 91, Step A; 350 mg, 1.55 mmol), (methylimino)(thioxo)methane (175 mg, 2.4 mmol), and pyridine (10 mL) stirred at 90 °C for 15 min. The mixture was cooled to room temperature, and charged with 1-cyclohexyl-3-(2-morpholino-ethyl)carbodiimide nitro-p-toluenesulfonate (1.23 g, 2.91 mmol). The mixture was stirred at 90 °C for 3 h. The mixture was cooled to room temperature and charged with Et_2O. The resulting precipitate was filtered and washed with Et_2O. The filtrate was concentrated to dryness, and the resulting crude purified by silica gel chromatography (0-10% CH_3CN/CH_2Cl_2, 30 min gradient; then 10% CH_3CN/CH_2Cl_2, 30 min) to afford the title compound as a yellow solid (269 mg, 66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 2.9 (d, *J*=4.6 Hz, 3 H) 3.2 (s, 3 H) 3.2 (t, *J*=6.0 Hz, 2 H) 4.1 (t, *J*=7.0 Hz, 2 H) 7.1 (q, *J*=4.6 Hz, 1 H) 7.3 (d, *J*=8.4 Hz, 1 H) 7.9 (dd, *J*=8.7, 2.3 Hz, 1 H) 8.0 (d, *J*=2.4 Hz, 1 H). ES-LCMS *m/z* 265 (100), (M+H).



Step C: N^2-methyl-1-[3-(methyloxy)propyl]-1*H*-benzimidazole-2,5-diamine

A mixture of *N*-methyl-1-[3-(methyloxy)propyl]-5-nitro-1*H*-benzimidazol-2-amine (Example 91, Step B; 269 mg, 1.02 mmol), 10% Pd/C (27 mg), and MeOH (30 mL) stirred under an atmosphere of H_2 (1 atm) for 5 h. The reaction was filtered over Celite, and the filtrate concentrated to dryness to

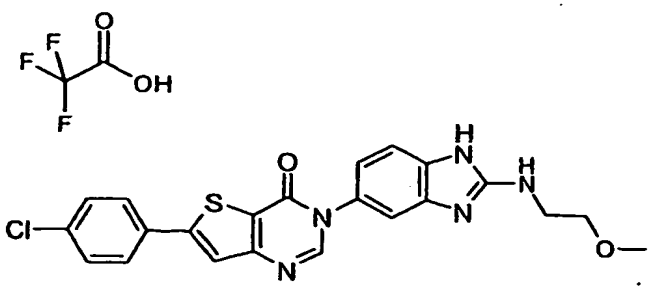
afford the title compound as a tan solid (230 mg, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 2.8 (d, *J*=4.7 Hz, 3 H) 3.2 (s, 3 H) 3.2 (t, *J*=6.2 Hz, 2 H) 3.8 (t, *J*=6.9 Hz, 2 H) 4.4 (s, 2 H) 6.2 (m, 2 H) 6.4 (d, *J*=1.9 Hz, 1 H) 6.7 (d, *J*=8.1 Hz, 1 H). ES-LCMS *m/z* 235 (100), (M+H).



Step D: 6-(4-chlorophenyl)-3-{2-(methylamino)-1-[3-(methyloxy)propyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of N^2-methyl-1-[3-(methyloxy)propyl]-1*H*-benzimidazole-2,5-diamine (Example 91, Step C; 230 mg, 0.98 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 317 mg, 0.98 mmol), and phenol (1 g) stirred at 200 °C for 1 h. The mixture was cooled to room temperature, charged with and 1 N NaOH (aq) (10 mL), then extracted with CH_2Cl_2. The organics were dried over $MgSO_4$ (anhy.), filtered, and the filtrate concentrated to dryness. The resulting crude was charged with DMSO (4 mL) and MeOH (20 mL). The resulting tan precipitate was filtered, washed with MeOH, then taken up in DMSO (2 mL) and a drop of TFA, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as a white solid (45 mg, 7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.9 (m, 2 H) 2.5 (s, 3 H) 3.1 (d, *J*=4.6 Hz, 3 H) 3.3 (t, *J*=6.0 Hz, 2 H) 4.2 (t, *J*=6.8 Hz, 2 H) 7.5 (dd, *J*=8.5, 1.9 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.6 (d, *J*=8.6 Hz, 1 H) 7.7 (d, *J*=1.8 Hz, 1 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.0 (s, 1 H). ES-LCMS *m/z* 480 (100), (M+H).

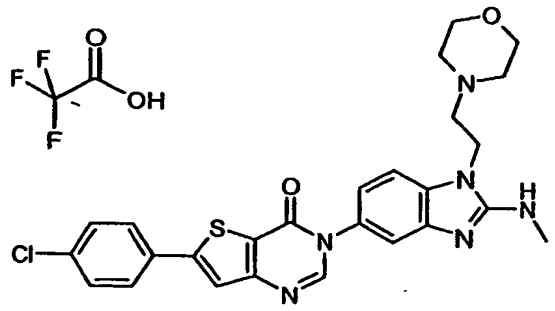
Example 92



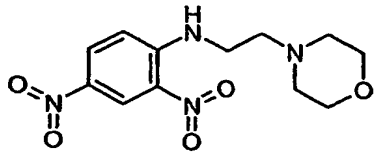
6-(4-chlorophenyl)-3-(2-{[2-(methyloxy)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting [2-(methyloxy)ethyl]amine (2 mL) for pyrrolidine and employing the techniques found in Example 86, Steps A, B, and C to afford a white solid (116 mg, 26% yield). ^{1}H NMR (300 MHz DMSO-d_6) δ 3.3 (m, 3 H) 3.6 (m, 4 H) 7.4 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.5 (d, *J*=8.6 Hz, 1 H) 7.6 (m, *J*=8.6 Hz, 3 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.2 (s, 1 H) 12.9 (s, 1 H). ES-LCMS *m/z* 452 (100), (M+H).

Example 93



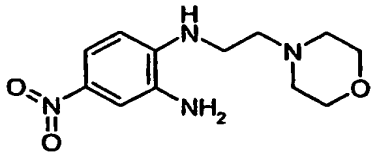
6-(4-chlorophenyl)-3-{2-(methylamino)-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: *N*-[2-(4-morpholinyl)ethyl]-2,4-dinitroaniline

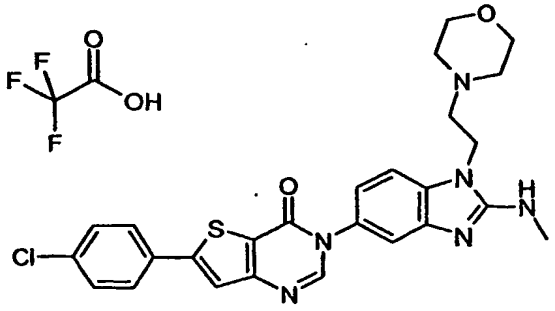
[2-(4-Morpholinyl)ethyl]amine (10.49 mL, 80.60 mmol) was added to a mixture of 1-fluoro-2,4-dinitrobenzene (5 g, 26.87 mmol) and EtOH (25 mL) at room

temperature. The mixture was then stirred at 90 °C in a pressure tube for 15 min. The mixture was cooled to room temperature, and the resulting precipitate was filtered, washed with EtOH, and air-dried to afford the title compound as an orange solid (7.56 mg, 95% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.5 (m, 2 H) 2.6 (t, *J*=6.2 Hz, 2 H) 3.6 (d, 8 H) 7.2 (d, *J*=9.7 Hz, 1 H) 8.3 (dd, *J*=9.7, 2.8 Hz, 1 H) 8.9 (d, *J*=2.8 Hz, 1 H) 9.1 (t, *J*=4.7 Hz, 1 H). ES-LCMS *m/z* 297 (90), (M+H).



Step B: *N*^{1}-[2-(4-morpholinyl)ethyl]-4-nitro-1,2-benzenediamine

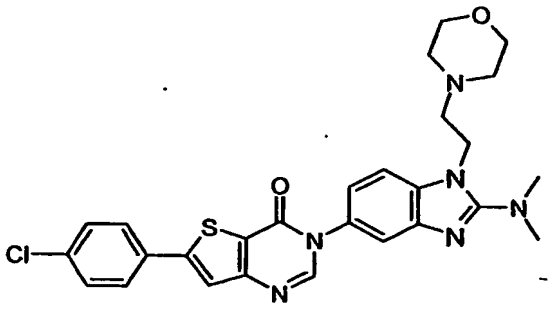
A solution of $Na_2S_2O_4$ (13.33 g, 76.56 mmol) in H_2O (50 mL) was added to a solution of *N*-[2-(4-morpholinyl)ethyl]-2,4-dinitroaniline (Example 93, Step A; 7.56 g, 25.52 mmol) in EtOH (100 mL) at reflux. The mixture stirred at reflux for 1.5 h. The mixture was filtered and the filtrate was concentrated to dryness. The resulting crude was purified by silica gel chromatography (0-7.5% MeOH/CH_2Cl_2 45 min gradient, then 10%MeOH/CH_2Cl_2, 45 min) to afford the title compound as an orange solid (2.18 g, 32% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.4 (m, 4 H) 2.6 (t, *J*=6.6 Hz, 2 H) 3.3 (m, 2 H) 3.6 (m, 4 H) 5.1 (s, 2 H) 5.8 (t, *J*=5.2 Hz, 1 H) 6.5 (d, *J*=8.8 Hz, 1 H) 7.4 (d, *J*=2.5 Hz, 1 H) 7.5 (dd, *J*=8.8, 2.8 Hz, 1 H). ES-LCMS *m/z* 265 (100), (M-H).



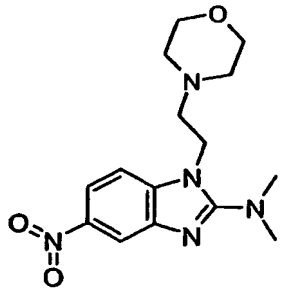
Step C: 6-(4-chlorophenyl)-3-{2-(methylamino)-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting N^1-[2-(4-morpholinyl)ethyl]-4-nitro-1,2-benzenediamine (Example 93, Step B; 400 mg, 1.5mmol) for N^1-[3-(methyloxy)propyl]-4-nitro-1,2-benzenediamine and employing the techniques found in Example 91, Steps B, C, and D to afford a tan solid (35 mg, 25% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.1 (s, 3 H) 3.7 (s, 8 H) 4.4 (s, 4 H) 7.5 (d, J=6.6 Hz, 1 H) 7.6 (d, J=8.8 Hz, 2 H) 7.7 (m, 2 H) 7.9 (d, J=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS m/z 522 (50), (M+H).

Example 94



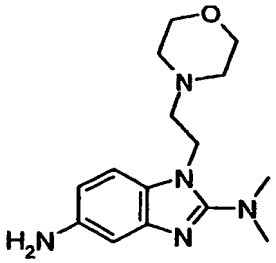
6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: *N*,*N*-dimethyl-1-[2-(4-morpholinyl)ethyl]-5-nitro-1*H*-benzimidazol-2-amine

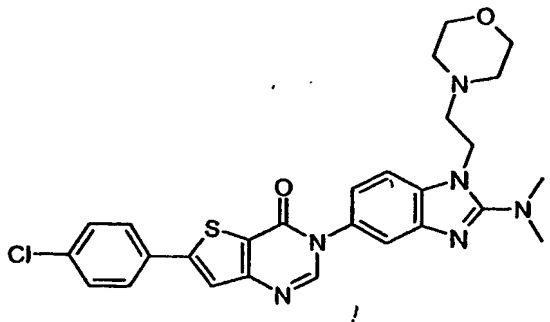
A mixture of N^1-[2-(4-morpholinyl)ethyl]-4-nitro-1,2-benzenediamine (Example 93, Step B; 300 mg, 1.13 mmol), *N*-(dichloromethylidene)-*N*-methylmethanaminium chloride (551 mg, 3.39 mmol), *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (1 mL), and CH_2Cl_2 (10 mL) stirred at reflux for 2 h. The mixture was cooled to room temperature, concentrated to dryness, and the resulting crude purified by silica gel chromatography (0-8%

MeOH/CH_2Cl_2, 30 min gradient; then 8% MeOH/CH_2Cl_2, 30 min) to afford the title compound as a yellow oil (305 mg, 85% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.4 (m, 4 H) 2.6 (t, *J*=6.7 Hz, 2 H) 3.0 (s, 6 H) 3.4 (m, 4 H) 4.2 (t, *J*=6.6 Hz, 2 H) 7.6 (d, *J*=8.8 Hz, 1 H) 8.0 (dd, *J*=8.8, 2.4 Hz, 1 H) 8.1 (d, *J*=2.2 Hz, 1 H). ES-LCMS *m/z* 320 (100), (M+H).



Step B: N^2,N^2-dimethyl-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazole-2,5-diamine

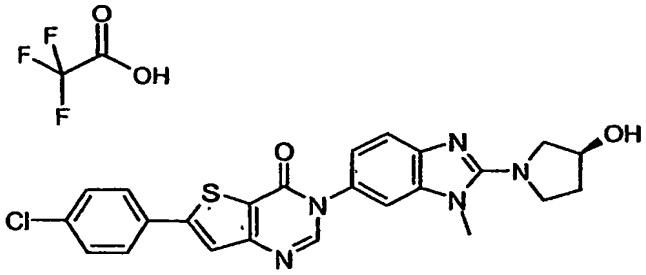
A mixture of *N*,*N*-dimethyl-1-[2-(4-morpholinyl)ethyl]-5-nitro-1*H*-benzimidazol-2-amine (Example 94, Step A; 305 mg, 0.96 mmol), 10% Pd/C (30 mg), and MeOH (20 mL) stirred under an atmosphere of H_2 (1 atm) for 30 min. The reaction was filtered over Celite, and the filtrate concentrated to dryness to afford the desired compound as a pink oil (226 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.4 (m, 4 H) 2.6 (t, *J*=7.0 Hz, 2 H) 2.8 (s, 6 H) 3.5 (m, 4 H) 4.0 (t, *J*=7.1 Hz, 2 H) 4.6 (s, 2 H) 6.4 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.6 (d, *J*=2.0 Hz, 1 H) 7.0 (d, *J*=8.4 Hz, 1 H). ES-LCMS *m/z* 290 (100), (M+H).



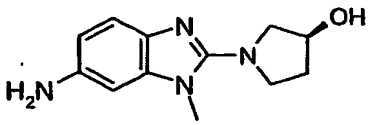
Step C: 6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

A mixture of N^2,N^2-dimethyl-1-[2-(4-morpholinyl)ethyl]-1*H*-benzimidazole-2,5-diamine (Example 94, Step B; 252 mg, 0.78 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 226 mg, 0.78 mmol), and phenol (1 g) stirred at 200 °C for 30 min. The mixture was cooled to room temperature, and the resulting crude purified by silica gel chromatography (CH_2Cl_2, 10 min, then 0-10% MeOH/CH_2Cl_2, 30 min gradient; then 10% MeOH/CH_2Cl_2, 30 min). The resulting product was triturated with MeOH to afford the title compound as a white solid (225 mg, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.4 (m, 4 H) 2.7 (t, *J*=6.8 Hz, 2 H) 3.0 (s, 6 H) 3.5 (m, 4 H) 4.2 (t, *J*=7.0 Hz, 2 H) 7.2 (dd, *J*=8.3, 2.1 Hz, 1 H) 7.5 (m, 2 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 535 (100), (M+).

Example 95



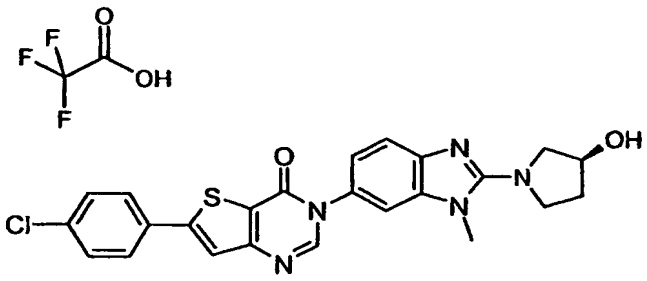
6-(4-chlorophenyl)-3-{2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-1-methyl-1*H*-benzimidazol-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate (salt)



Step A: (3*S*)-1-(6-amino-1-methyl-1*H*-benzimidazol-2-yl)-3-pyrrolidinol

A mixture of 2-chloro-1-methyl-1*H*-benzimidazol-6-amine (Example 11, Step C; 200 mg, 1.1 mmol), (3*S*)-3-pyrrolidinol (444 μL), and EtOH (10 mL) stirred in a pressure tube at 160 °C for 17 h. The reaction was and concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-10% 2M ammonia in MeOH/CH_2Cl_2, 20 min gradient, then 10% 2M ammonia

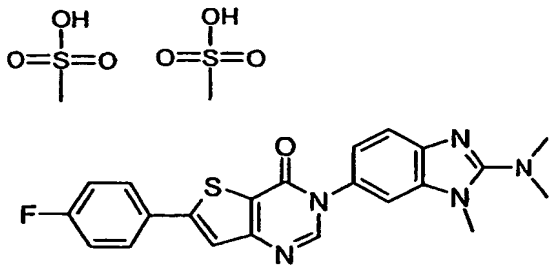
in MeOH/CH_2Cl_2, 20 min) to afford the title compound as a tan solid (233 mg, 91% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.8 (m, 1 H) 2.0 (m, 1 H) 3.3 (dd, *J*=10.3, 1.6 Hz, 1 H) 3.4 (m, 4 H) 3.6 (m, 2 H) 4.3 (d, *J*=2.4 Hz, 1 H) 4.6 (s, 2 H) 4.9 (d, *J*=3.4 Hz, 1 H) 6.3 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.4 (d, *J*=2.1 Hz, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 233 (100), (M+H).



Step B: 6-(4-chlorophenyl)-3-{2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-1-methyl-1*H*-benzimidazol-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of (3*S*)-1-(6-amino-1-methyl-1*H*-benzimidazol-2-yl)-3-pyrrolidinol (Example 95, Step A; 217 mg, 0.93 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 302 mg, 0.93 mmol), and phenol (1 g) stirred at 200 °C for 30 min. The mixture was cooled to 60 °C and charged with MeOH. The resulting precipitate was filtered, washed with MeOH, then taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as a white solid (91 mg, 17% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.0 (m, 2 H) 3.6 (d, *J*=10.1 Hz, 1 H) 3.8 (s, 3 H) 3.9 (m, 3 H) 4.5 (s, 1 H) 5.3 (s, 1 H) 7.4 (d, *J*=7.9 Hz, 1 H) 7.5 (m, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.9 (s, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). ES-LCMS *m/z* 478 (100), (M+H).

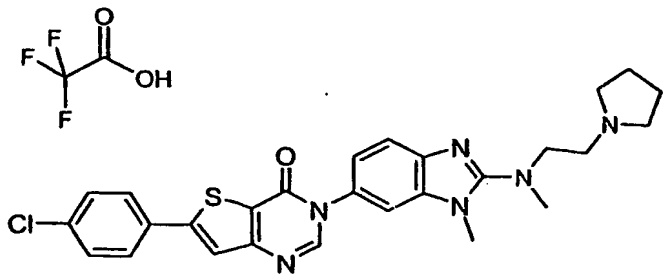
Example 96



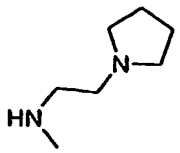
3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]-6-(4-fluorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one dimethanesulfonate

A mixture of N^2,N^2,1-trimethyl-1*H*-benzimidazole-2,6-diamine (Example 11, Step D; 165 mg, 0.88 mmol), methyl 3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-(4-fluorophenyl)-2-thiophenecarboxylate (made by substituting 3-amino-5-(4-fluorophenyl)-2-thiophenecarboxylate for 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate in Example 1, Step D; 270 mg, 0.88 mmol), stirred in phenol (1 g) from room temperature to 150 °C over 30 min, then at 150 °C for 1 h. The mixture was cooled to 60 °C and poured into MeOH. The resulting precipitate was filtered and washed with MeOH. The precipitate was taken up in CH_2Cl_2 and a few drops of MeOH, then charged with methane sulfonic acid (2 equivalents). The mixture was concentrated to dryness, then triturated with CH_2Cl_2 to afford the title compound as a yellow solid (260 mg, 49% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (s, 6 H) 3.3 (s, 6 H) 3.8 (t, 3 H) 7.4 (t, *J*=8.8 Hz, 2 H) 7.5 (m, 1 H) 7.6 (m, 1 H) 8.0 (m, 4 H) 8.5 (s, 1 H). ES-LCMS *m/z* 420 (100), (M+H).

Example 97

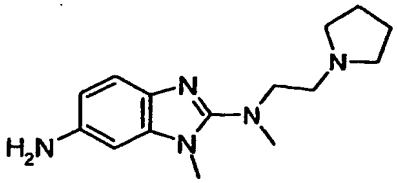


6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-6-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate



Step A: *N*-methyl-2-(1-pyrrolidinyl)ethanamine

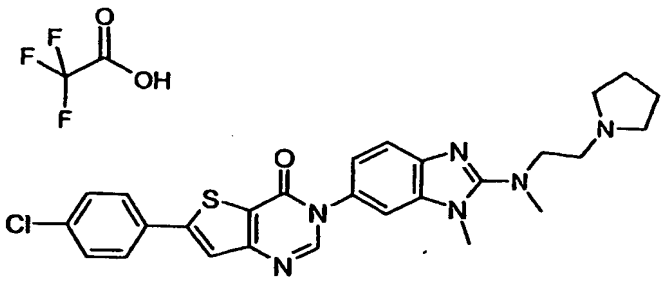
A solution of 1-(2-chloroethyl)pyrrolidine (10 g, 58.8 mmol) in H_2O (15 mL) was added drop-wise to a solution of 40% methylamine in H_2O (46 mL) at room temperature over 30 min. The reaction stirred at room temperature for 2 h. The reaction was then charged with additional 40% methylamine in H_2O (20 mL) and stirred at room temperature for 19 h. NaOH (18.5 g, 462.5 mmol) was added to the mixture portion-wise at room temperature. The reaction was cooled to room temperature, then extracted with Et_2O. The organics were dried over $MgSO_4$ (anhy.), filtered, and the filtrate was concentrated to dryness to afford the title compound as a gold liquid (6.64 g, 88% yield). ^1H NMR (300 MHz, DMSO-d_6) δ 1.7 (m, 5 H) 2.3 (s, 3 H) 2.5 (m, 8 H). ES-LCMS *m/z* 129 (100), (M+H).



Step B: N^2,1-dimethyl-N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,6-diamine

A mixture of 2-chloro-1-methyl-1*H*-benzimidazol-6-amine (Example 11, Step C; 200 mg, 1.1 mmol), *N*-methyl-2-(1-pyrrolidinyl)ethanamine (Example 97, Step A; 282 mg, 2.2 mmol), and EtOH (10 mL) stirred in a pressure tube at 160 °C for 22 h. The reaction was cooled to room temperature, charged with additional *N*-methyl-2-(1-pyrrolidinyl)ethanamine (423 mg, 3.3 mmol) and stirred at 160 °C for 24 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (10% 2 M ammonia

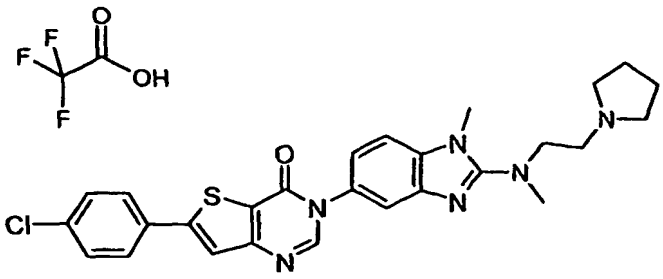
in $MeOH/CH_2Cl_2$) to afford the title compound as a gold oil (168 mg, 56% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 1.6 (s, 4 H) 2.5 (s, 4 H) 2.6 (t, *J*=7.0 Hz, 2 H) 2.9 (s, 3 H) 3.3 (m, 2 H) 3.3 (s, 2 H) 3.5 (d, 3 H) 6.4 (d, *J*=8.3 Hz, 1 H) 6.5 (s, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 274 (100), (M+H).



Step C: 6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-6-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

A mixture of N^2,1-dimethyl-N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,6-diamine (Example 97, Step B; 168 mg, 0.61 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 198 mg, 0.61 mmol), and phenol (1 g) stirred from room temperature to 150 °C over 30 min, then at 150 °C for 1 h. The mixture was cooled to room temperature then purified by silica gel chromatography (CH_2Cl_2, 10 min, then 0-10% 2 M ammonia in $MeOH/CH_2Cl_2$, 30 min gradient; then 10% 2 M ammonia in $MeOH/CH_2Cl_2$, 30 min). The resulting product was taken up in DMSO, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5 min gradient) to afford the title compound as a white solid (90 mg, 23% yield). ^1H NMR (300 MHz, DMSO-d_6) δ 2.0 (s, 4 H) 3.2 (s, 3 H) 3.4 (s, 4 H) 3.5 (t, *J*=5.9 Hz, 2 H) 3.8 (m, 5 H) 7.3 (dd, *J*=8.3, 1.9 Hz, 1 H) 7.6 (m, 3 H) 7.8 (d, *J*=1.9 Hz, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). ES-LCMS *m/z* 519 (100), (M+).

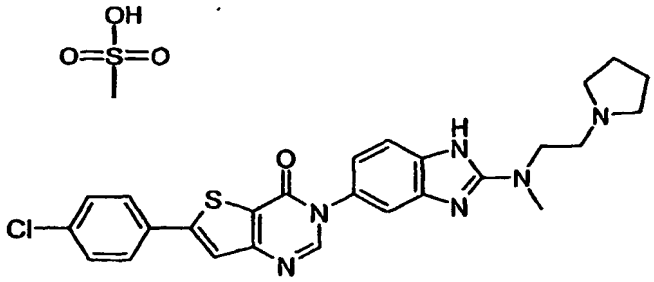
Example 98



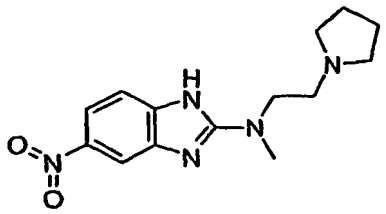
6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

The title compound was synthesized by substituting 2-chloro-1-methyl-1*H*-benzimidazol-5-amine (Example 11, Step C; 200 mg, 1.1 mmol), for 2-chloro-1-methyl-1*H*-benzimidazol-6-amine, and employing the techniques found in Example 97, Steps B and C to afford a white solid (105 mg, 19% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.9 (s, 4 H) 3.1 (s, 3 H) 3.3 (s, 4 H) 3.5 (t, *J*=6.0 Hz, 2 H) 3.7 (m, 5 H) 7.3 (dd, *J*=8.4, 1.9 Hz, 1 H) 7.6 (m, 4 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 519 (100), (M+).

Example 99

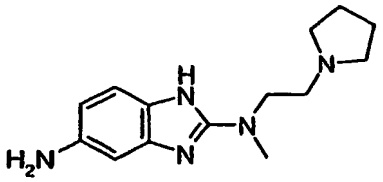


6-(4-chlorophenyl)-3-(2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate



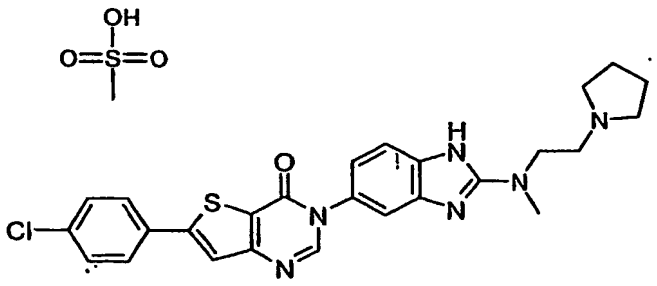
Step A: *N*-methyl-5-nitro-*N*-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-2-amine

A mixture of 2-chloro-5-nitro-1*H*-benzimidazole (Example 75, Step A; 250 mg, 1.27 mmol), *N*-methyl-2-(1-pyrrolidinyl)ethanamine (Example 97, Step A; 244 mg, 1.91 mmol), and MeOH (10 mL) stirred in a pressure tube at 150 °C for 22 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-5% MeOH/CH_2Cl_2, 20 min gradient; then 5% MeOH/CH_2Cl_2, 10 min) to afford the title compound as a yellow solid (282 mg, 77% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.7 (s, 4 H) 3.1 (s, 3 H) 3.3 (s, 6 H) 3.7 (s, 2 H) 7.3 (d, *J*=8.8 Hz, 1 H) 7.9 (m, 2 H). APCI-LCMS *m/z* 290 (100), (M+H).



Step B: N^2-methyl-N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,5-diamine

A mixture of *N*-methyl-5-nitro-*N*-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-2-amine (Example 99, Step A; 282 mg, 0.97 mmol), 10% Pd/C (28 mg), and EtOH (15 mL) stirred under an atmosphere of H_2 (1 atm) for 2.5 h. The reaction was filtered over Celite, and the filtrate concentrated to dryness to afford the title compound as a brown solid (247 mg, 98% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.7 (m, 4 H) 2.7 (m, *J*=5.5, 5.5 Hz, 4 H) 2.8 (t, *J*=6.5 Hz, 2 H) 3.0 (s, 3 H) 3.6 (t, *J*=6.6 Hz, 2 H) 6.2 (dd, *J*=8.3, 1.9 Hz, 1 H) 6.5 (d, *J*=1.9 Hz, 1 H) 6.8 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 260 (100), (M+H).

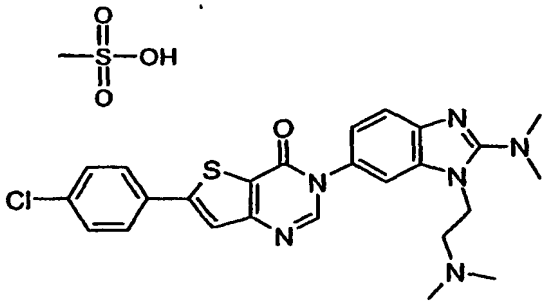


Step C: 6-(4-chlorophenyl)-3-(2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-

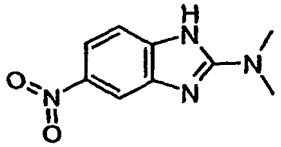
benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

A mixture of N^2-methyl-N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,5-diamine (Example 99, Step B; 226 mg, 0.87 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 282 mg, 0.87 mmol), and phenol (1 g) stirred from room temperature to 120 °C over 30 min, then at 120 °C for 30 min. The mixture was cooled to room temperature then purified by silica gel chromatography (CH_2Cl_2, 10min, then 0-10% 2 M ammonia in MeOH/CH_2Cl_2, 30 min gradient). The resulting product was taken up in CH_2Cl_2 and charged with methane sulfonic acid (19 μL). The resulting precipitate was filtered, washed with CH_2Cl_2, and high-vac dried to afford the title compound as an off-white solid (60 mg, 20% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.0 (s, 4 H) 2.4 (s, 6 H) 3.3 (s, 3 H) 3.6 (t, *J*=5.2 Hz, 2 H) 3.7 (s, 4 H) 4.0 (t, *J*=5.5 Hz, 2 H) 7.4 (d, *J*=8.6 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 3 H) 7.7 (s, 1 H) 8.0 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). APCI-LCMS *m/z* 505 (100), (M+).

Example 100

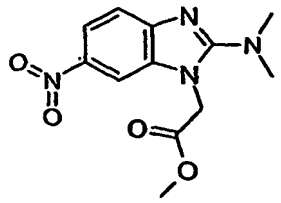


6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate



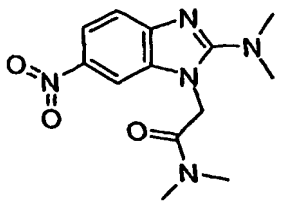
Step A: *N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine

A mixture of 2-chloro-5-nitro-1*H*-benzimidazole (Example 75, Step A; 1 g, 5.06 mmol) and 2 M dimethylamine in MeOH (10 mL) stirred at 160 °C in a pressure tube for 1 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-5% $MeOH/CH_2Cl_2$, 30 min gradient; 5% $MeOH/CH_2Cl_2$, 30 min) to afford the title compound as a yellow solid (846 mg, 81% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 3.1 (s, 6 H) 7.2 (d, *J*=9.0 Hz, 1 H) 7.9 (m, *J*=9.7 Hz, 2 H) 11.8 (s, 1 H). ES-LCMS *m/z* 207 (100), (M+H).



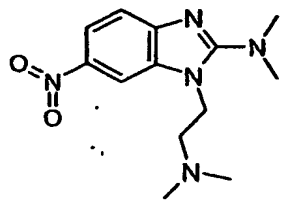
Step B: methyl [2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]acetate

NaH (1.26g, 31.53mmol) was added to a solution of *N*,*N*-dimethyl-5-nitro-1*H*-benzimidazol-2-amine (Example 100, Step A; 5 g, 24.25 mmol) in DMF (50 mL) at room temperature. The mixture was stirred at room temperature for 30 min. The reaction was charged with methyl bromoacetate (2.52 mL, 26.67 mmol) and stirred at room temperature for 16 h. The reaction was concentrated to dryness and the resulting residue was purified by silica gel chromatography (0-4% $MeOH/CH_2Cl_2$, 30 min gradient; then 4% $MeOH/CH_2Cl_2$, 30 min). The resulting compounds were separated by chiral prep HPLC chromatography to afford the title compound as a yellow solid (2.5 g, 37% yield). ^1H NMR (400 MHz DMSO-d_6) δ 3.0 (s, 6 H) 3.7 (s, 3 H) 5.2 (s, 2 H) 7.4 (d, *J*=8.8 Hz, 1 H) 8.0 (d, *J*=11.0 Hz, 1 H) 8.3 (d, *J*=2.1 Hz, 1 H). APCI-LCMS *m/z* 279 (100), (M+H).



Step C: 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]-*N*,*N*-dimethylacetamide

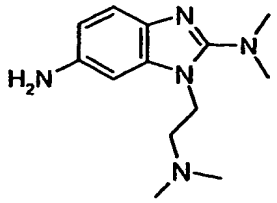
A mixture of methyl [2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]acetate (Example 100, Step B; 300 mg, 1.08 mmol) and 2 M dimethylamine in MeOH (10 mL) stirred at 120 °C in a pressure tube for 30 min, then at 80 °C for 19.5 h. The reaction was cooled to room temperature and the resulting precipitate filtered off. The filtrate was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-5% MeOH/CH_2Cl_2, 20 min gradient) to afford the title compound as a yellow solid (180 mg, 51% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.9 (s, 3 H) 3.0 (s, 6 H) 3.1 (s, 3 H) 5.2 (s, 2 H) 7.4 (d, *J*=8.8 Hz, 1 H) 8.0 (d, *J*=8.8 Hz, 1 H) 8.1 (s, 1 H). ES-LCMS *m/z* 292 (100), (M+H).



Step D: 1-[2-(dimethylamino)ethyl]-*N*,*N*-dimethyl-6-nitro-1*H*-benzimidazol-2-amine

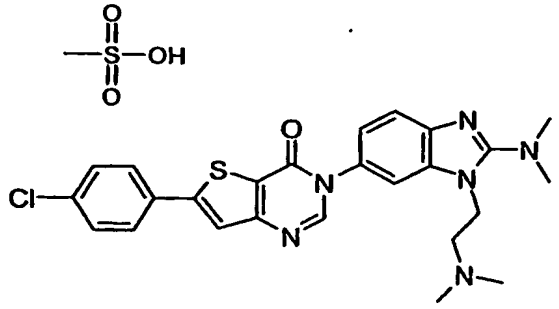
AlH_3 (1 M) in THF (3.1 mL, 3.1 mmol) was added drop-wise to a suspension of 2-[2-(dimethylamino)-6-nitro-1*H*-benzimidazol-1-yl]-*N*,*N*-dimethylacetamide (Example 100, Step C; 180 mg, 0.62 mmol) in THF (10 mL) at 0 °C. The reaction was stirred at room temperature for 1 h. The reaction was poured into 1 N NaOH (aq) at 0 °C and then extracted with CH_2Cl_2. The organics were dried over $MgSO_4$ (anhy.), filtered, and concentrated to dryness. The resulting residue was purified by silica gel chromatography (0-5% 2 M ammonia in MeOH/CH_2Cl_2, 15 min gradient; then 5% 2M ammonia in MeOH/CH_2Cl_2, 15 min) to afford the title compound as a yellow oil (95 mg, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.2 (s, 6 H) 2.6 (t, *J*=6.6 Hz, 2 H) 3.1 (s, 6 H) 4.3 (t, *J*=6.6 Hz, 2 H) 7.4 (d, *J*=8.8 Hz, 1 H) 8.0 (dd, *J*=8.8, 2.2 Hz,

1 H) 8.3 (s, 1 H). ES-LCMS *m/z* 278 (100), (M+H).



Step E: 1-[2-(dimethylamino)ethyl]-N^2,N^2-dimethyl-1*H*-benzimidazole-2,6-diamine

A mixture of 1-[2-(dimethylamino)ethyl]-*N*,*N*-dimethyl-6-nitro-1*H*-benzimidazol-2-amine (Example 100, Step D; 92 mg, 0.33 mmol), 10% Pd/C (10 mg), and EtOH (10 mL) stirred under an atmosphere of H_2 (1 atm) for 30 min. The reaction was filtered over celite, and the filtrate concentrated to dryness to afford the title compound as a gold oil (77 mg, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.2 (s, 6 H) 2.6 (t, *J*=7.3 Hz, 2 H) 2.8 (s, 6 H) 4.0 (m, 2 H) 4.8 (s, 2 H) 6.4 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.5 (s, 1 H) 7.0 (d, *J*=8.4 Hz, 1 H). ES-LCMS *m/z* 248 (100), (M+H).

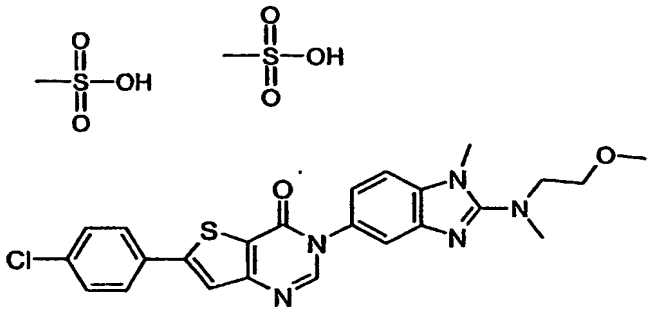


Step F: 6-(4-chlorophenyl)-3-{2-(dimethylamino)-1-[2-(dimethylamino)ethyl]-1*H*-benzimidazol-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one methanesulfonate

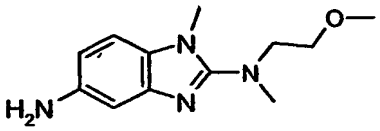
A mixture of 1-[2-(dimethylamino)ethyl]-N^2,N^2-dimethyl-1*H*-benzimidazole-2,6-diamine (Example 100, Step E; 77mg, 0.31mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 100 mg, 0.31 mmol), and phenol (1 g) stirred from room temperature to 120 °C over 30 min, then at 120 °C for 30 min. The mixture

was cooled to room temperature then purified by silica gel chromatography (CH_2Cl_2, 15 min, then 0-10% 2M ammonia in MeOH/CH_2Cl_2, 30 min gradient). The resulting product was taken up in CH_2Cl_2 and charged with methane sulfonic acid (18 μL). The solution was charged with Et_2O and the resulting precipitate was filtered, washed with Et_2O, and air-dried to afford the title compound as an off-white solid (28 mg, 13% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.3 (s, 6 H) 2.9 (m, *J*=4.5 Hz, 6 H) 3.6 (m, 2 H) 3.7 (s, 6 H) 4.6 (m, 2 H) 7.5 (d, *J*=8.1 Hz, 1 H) 7.6 (m, 3 H) 7.9 (m, 3 H) 8.0 (s, 1 H) 8.5 (s, 1 H). APCI-LCMS *m/z* 492 (100), (M-H).

Example 101



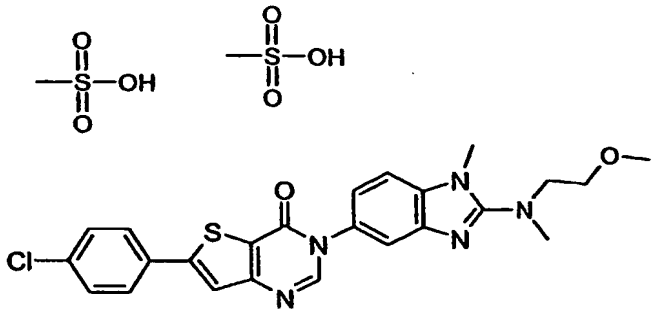
6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(methyloxy)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one dimethanesulfonate



Step A: N^2,1-dimethyl-N^2-[2-(methyloxy)ethyl]-1*H*-benzimidazole-2,5-diamine

A mixture of 2-chloro-1-methyl-1*H*-benzimidazol-5-amine (Example 11, Step C; 200 mg, 1.1mmol), *N*-methyl-2-(methyloxy)ethanamine (1.2 mL, 11 mmol), and EtOH (10 mL) was stirred in a pressure tube at 160 °C for 25 h. The reaction was charged with additional *N*-methyl-2-(methyloxy)ethanamine (0.6 mL, 5.5 mmol) and stirred in a pressure tube at 160 °C for 24 h. The reaction was concentrated to dryness, and the resulting crude was purified by silica gel chromatography (0-5% 2 M ammonia in MeOH/CH_2Cl_2, 20 min gradient) to

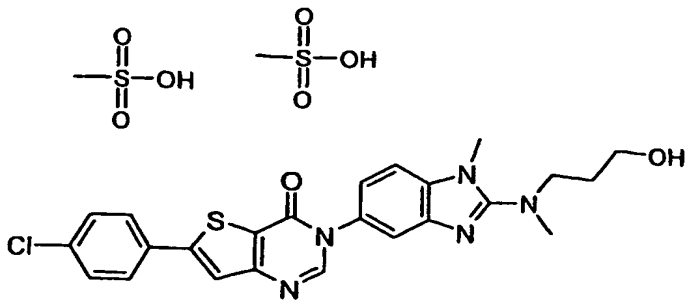
afford the title compound as a brown oil (218 mg, 85% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.9 (s, 3 H) 3.3 (s, 3 H) 3.3 (m, 2 H) 3.5 (s, 3 H) 3.6 (t, *J*=5.7 Hz, 2 H) 4.6 (s, 2 H) 6.4 (dd, *J*=8.3, 1.9 Hz, 1 H) 6.6 (d, *J*=1.9 Hz, 1 H) 6.9 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 235 (100), (M+H).



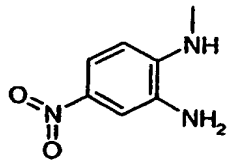
Step B: 6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(methyloxy)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one dimethanesulfonate

A mixture of N^2,1-dimethyl-N^2-[2-(methyloxy)ethyl]-1*H*-benzimidazole-2,5-diamine (Example 101, Step A; 218 mg, 0.93 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 300 mg, 0.93 mmol), and phenol (1 g) stirred from room temperature to 120°C over 30 min, then at 120 °C for 1 h. The reaction was cooled to 60 °C, poured into MeOH, and the resulting precipitate was filtered, washed with MeOH, and air-dried. The precipitate was taken up in DMSO and 3 drops of TFA, and purified by C18 preparative HPLC (1-99% CH_3CN/H_2O 5min gradient). The resulting compound was purified by silica gel chromatography (CH_2Cl_2, 5 min; then 0-5% 2M ammonia in MeOH/CH_2Cl_2, 20min gradient). The resulting compound was taken up in CH_2Cl_2 and treated with methane sulfonic acid (0.03 mL). The mixture was concentrated to dryness to afford the title compound as a white solid (145 mg, 23% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.3 (s, 6 H) 3.3 (s, 3 H) 3.3 (s, 3 H) 3.7 (t, *J*=5.0 Hz, 2 H) 3.8 (t, *J*=5.0 Hz, 2 H) 3.9 (s, 3 H) 7.6 (m, 3 H) 7.7 (d, *J*=1.7 Hz, 1 H) 7.8 (d, *J*=8.6 Hz, 1 H) 8.0 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.5 (s, 1 H). ES-LCMS *m/z* 480 (100), (M+H).

Example 102

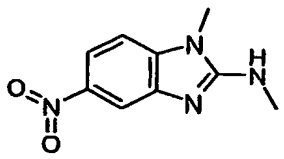


6-(4-chlorophenyl)-3-{2-[(3-hydroxypropyl)(methyl)amino]-1-methyl-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one dimethanesulfonate



Step A: N^1-methyl-4-nitro-1,2-benzenediamine

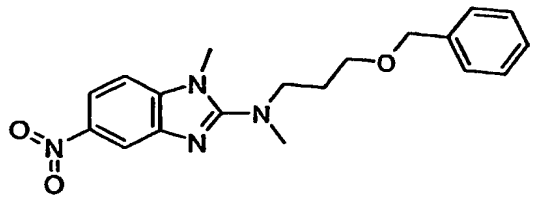
A solution of 2-fluoro-5-nitroaniline (10 g, 6.41 mmol) in MeOH (50 mL) was added drop-wise to a solution of 2 M dimethylamine in MeOH (100 mL) at room temperature. The reaction was stirred in a pressure tube at 140 °C for 8 h, then at room temperature for 70 h. The reaction cooled to room temperature, concentrated, and the resulting crude purified by silica gel chromatography (CH_2Cl_2) to afford the title compound as a red solid (7.6 g, 71% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.8 (d, *J*=5.0 Hz, 3 H) 5.1 (s, 2 H) 6.1 (d, *J*=4.7 Hz, 1 H) 6.4 (d, *J*=9.1 Hz, 1 H) 7.4 (d, *J*=2.5 Hz, 1 H) 7.6 (dd, *J*=8.8, 2.5 Hz, 1 H). ES-LCMS *m/z* 166 (100), (M-H).



Step B: *N*,1-dimethyl-5-nitro-1*H*-benzimidazol-2-amine

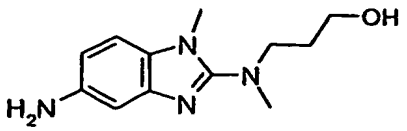
A mixture of N^1-methyl-4-nitro-1,2-benzenediamine (Example 102, Step A; 5 g, 29.9 mmol), (methylimino)(thioxo)methane (2.34 g, 32.0 mmol), and

pyridine (40 mL) stirred at 90 °C for 5 min. The mixture was cooled to room temperature and charged with 1-cyclohexyl-3-(2-morpholino-ethyl)carbodiimide nitro-p-toluenesulfonate (16.48 g, 38.9 mmol). The mixture was stirred at 90 °C for 3 h, cooled to room temperature, then charged with Et_2O. The resulting precipitate was stirred in EtOAc (300 mL), filtered, and washed with EtOAc. The precipitate was stirred in MeOH at room temperature for 12 h, filtered, and the MeOH filtrate was concentrated to dryness. The resulting crude filtrate was purified by silica gel chromatography (0-20% CH_3CN/CH_2Cl_2, 90 min gradient) to afford the title compound as an orange solid (4 g, 69% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.0 (d, *J*=4.7 Hz, 3 H) 3.6 (s, 3 H) 7.2 (q, *J*=4.4 Hz, 1 H) 7.3 (d, *J*=8.8 Hz, 1 H) 7.9 (dd, *J*=8.8, 2.2 Hz, 1 H) 8.0 (d, *J*=2.2 Hz, 1 H). ES-LCMS *m/z* MS 207 (100), (M+H).



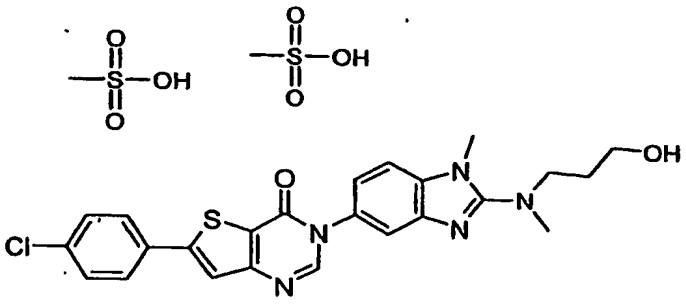
Step C: *N*,1-dimethyl-5-nitro-*N*-{3-[(phenylmethyl)oxy]propyl}-1*H*-benzimidazol-2-amine

NaH (48mg, 1.2mmol) was added to a solution of *N*,1-dimethyl-5-nitro-1*H*-benzimidazol-2-amine (Example 102, Step B; 206 mg, 1.0 mmol) in DMF (5 mL) at 0 °C. The mixture stirred at 0 °C for 15 min, and {[(3-bromopropyl)oxy]methyl}benzene (177 µL, 1.0 mmol) was added drop-wise at 0 °C. The reaction was stirred at room temperature for 2 h, quenched with MeOH, then concentrated to dryness. The resulting crude was purified by silica gel chromatography (CH_2Cl_2) to afford the title compound as a yellow oil (280 mg, 79% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.9 (m, 2 H) 3.0 (s, 3 H) 3.5 (m, 4 H) 3.7 (s, 3 H) 4.4 (s,.2 H) 7.3 (m, 5 H) 7.5 (d, *J*=8.8 Hz, 1 H) 8.0 (dd, *J*=8.7, 2.3 Hz, 1 H) 8.2 (d, *J*=2.2 Hz, 1 H). ES-LCMS *m/z* 354 (100), (M+2H).



Step D: 3-[(5-amino-1-methyl-1*H*-benzimidazol-2-yl)(methyl)amino]-1-propanol

A mixture *N*,1-dimethyl-5-nitro-*N*-{3-[(phenylmethyl)oxy]propyl}-1*H*-benzimidazol-2-amine (Example 102, Step C; 280 mg, 0.79 mmol), 10% Pd/C (28 mg), and EtOH (20 mL) stirred under 40 psi of H_2 for 42 h. The reaction was filtered over Celite and new 10% Pd/C (50 mg) was added. The reaction stirred under 55 psi of H_2 for 72 h. The reaction was charged with additional 10% Pd/C (50 mg), and stirred under 55 psi of H_2 for 28.5 h. The reaction was filtered over Celite, and the filtrate concentrated to dryness to afford the title compound as a pale oil (164 mg, 89% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.7 (m, 2 H) 2.9 (s, 3 H) 3.3 (m, 2 H) 3.4 (t, *J*=6.2 Hz, 2 H) 3.5 (s, 3 H) 4.9 (s, 2 H) 6.4 (dd, *J*=8.3, 2.2 Hz, 1 H) 6.6 (d, *J*=1.9 Hz, 1 H) 7.0 (d, *J*=8.3 Hz, 1 H). ES-LCMS *m/z* 236 (100), (M+2H).

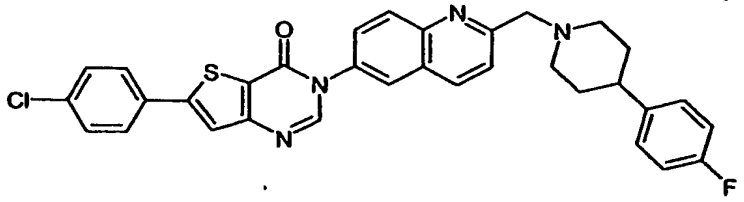


Step E: 6-(4-chlorophenyl)-3-(1-methyl-2-{methyl[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one trifluoroacetate

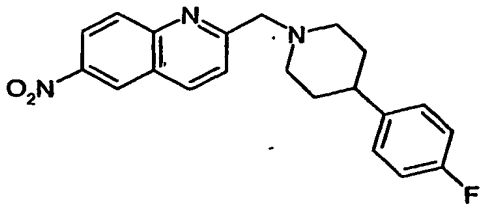
A mixture 3-[(5-amino-1-methyl-1*H*-benzimidazol-2-yl)(methyl)amino]-1-propanol (Example 102, Step D; 164 mg, 0.7 mmol), methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 226mg, 0.7mmol), and phenol (1

g) stirred from room temperature to 130 °C over 15 min, then at 130 °C for 1 h. The mixture was cooled to room temperature then purified by silica gel chromatography (0-5% MeOH/CH_2Cl_2, 30min, then 5% MeOH/CH_2Cl_2, 10 min gradient). The resulting product was taken up in CH_2Cl_2, charged with methane sulfonic acid (38 μL), then concentrated to dryness to afford the title compound as a tan solid (86 mg, 18% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.8 (m, 2 H) 2.3 (s, 6 H) 3.3 (s, 3 H) 3.5 (t, *J*=5.8 Hz, 2 H) 3.7 (t, *J*=7.0 Hz, 2 H) 3.8 (s, 3 H) 7.5 (dd, *J*=8.6, 1.6 Hz, 1 H) 7.6 (d, *J*=8.6 Hz, 2 H) 7.7 (s, 1 H) 7.8 (d, *J*=8.8 Hz, 2 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H). ES-LCMS *m/z* 400 (100), (M+H).

Example 103



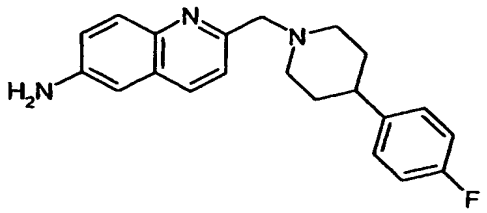
6-(4-chlorophenyl)-3-(2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}-6-nitroquinoline

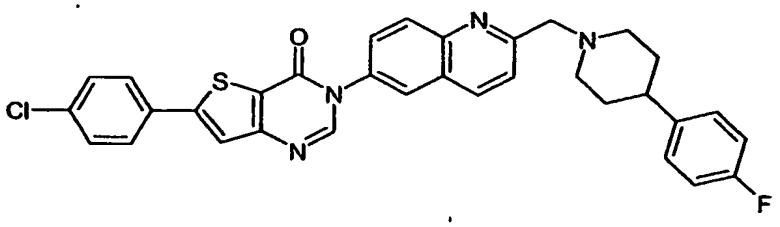
2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}-6-nitroquinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with 4-(4-fluorophenyl)piperidine. The desired compound was purified by column chromatography on silica gel, eluting with a gradient of 70% ethyl acetate in hexane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.74 (d, J = 8.6 Hz, 1H), 8.50 (d, J = 9.8 Hz, 1H), 8.22 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 7.35 – 7.10 (m, 4H), 3.89 (s,

2H), 3.65 (m, 1H), 3.21 (m, 2H), 2.97 (m, 2H), 1.87 (m, 4H); ES-LCMS *m/z* 366 (M+H).



Step B: 2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-amine

2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}-6-nitroquinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.63 (m, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.33 – 7.10 (m, 4H), 5.59 (brs, 2H) 3.89 (s, 2H), 3.62 (m, 1H), 3.37 (m, 2H), 2.98 (m, 2H), 2.64 (m, 2H), 1.86 (m, 2H); ES-LCMS 336 *m/z* (M+H).

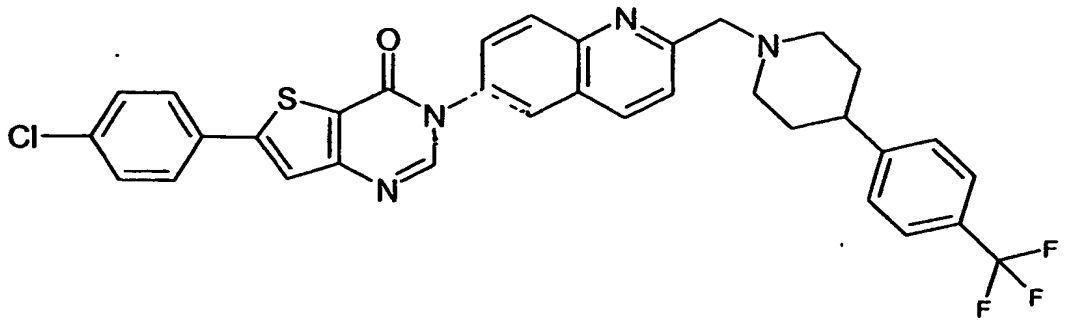


Step C: 6-(4-chlorophenyl)-3-(2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

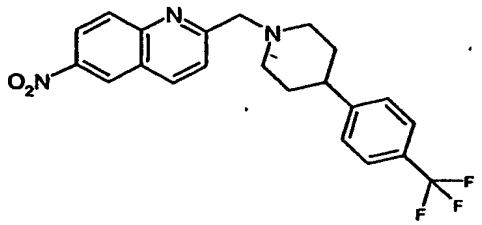
The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-{[4-(4-fluorophenyl)piperidin-1-yl]methyl}quinolin-6-amine (Example 4, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.36 (s, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.07 – 7.91 (m, 8H), 7.65 (d, J = 8.7 Hz, 1H),

7.33 (m, 1H), 7.17 (m, 2H), 3.87 (s, 2H), 3.04 (m, 3H), 2.80 (m, 2H), 2.26 (m, 2H), 1.84 (m, 2H); ES-LCMS *m/z* 581 (M+H).

Example 104

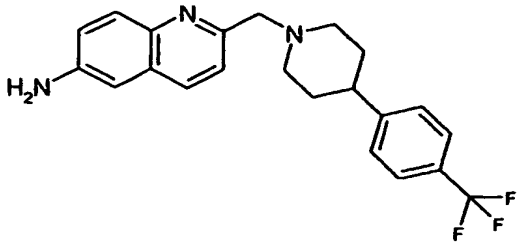


6-(4-chlorophenyl)-3-[2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



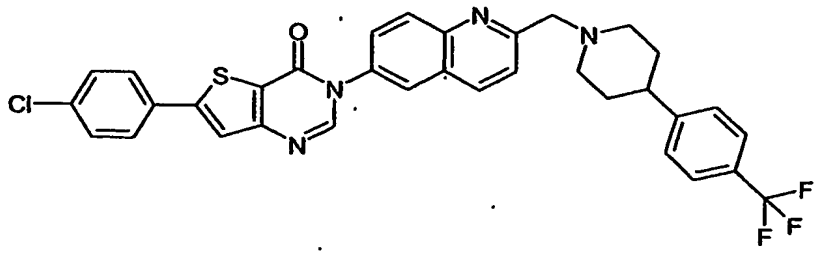
Step A: 6-nitro-2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinoline

6-nitro-2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with 4-(4-fluorophenyl)piperidine. The desired compound was purified by column chromatography on silica gel, eluting with a gradient of 70% ethyl acetate in hexane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.75 (d, J = 8.6 Hz, 1H), 8.50 (d, J = 9.3 Hz, 1H), 8.23 (d, J = 9.3 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 7.35 – 7.10 (d, J = 8.1 Hz, 2H), 3.90 (s, 2H), 3.68 (m, 1H), 3.23 (m, 2H), 2.98 (m, 2H), 1.87 (m, 4H); ES-LCMS *m/z* 416 (M+H).



Step B: 2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-amine

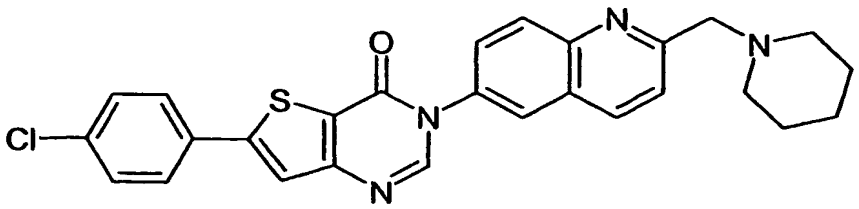
2-({4-[4-(Trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 6-nitro-2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (d, J = 8.6 Hz, 1H), 7.73 (m, 3H), 7.69 (m, 3H), 7.16 (m, 1H)), 5.60 (brs, 2H), 3.91 (s, 2H), 3.64 (m, 1H), 3.38 (m, 2H), 3.01 (m, 2H), 2.61 (m, 3H), 1.89 (m, 2H); ES-LCMS *m/z* 386 (M+H).



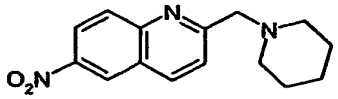
Step C: 6-(4-chlorophenyl)-3-[2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-({4-[4-(trifluoromethyl)phenyl]piperidin-1-yl}methyl)quinolin-6-amine (Example 4, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.48 (d, J = 8.6 Hz, 1H), 8.24 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 8.11 – 7.81 (m, 8H), 7.83 (d, J = 8.6 Hz, 1H), 7.70 – 7.38 (m, 2H), 3.89 (s, 2H), 3.03 (m, 3H), 2.75 (m, 2H), 2.24 (m, 2H) 1.81 (m, 2H); ES-LCMS *m/z* 631 (M+H).

Example 105

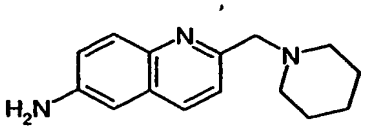


6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



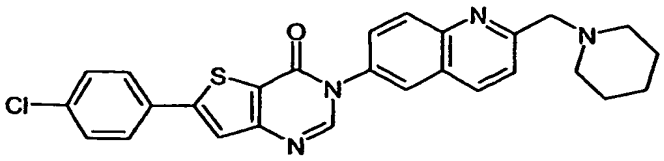
Step A: 6-nitro-2-(piperidin-1-ylmethyl)quinoline

6-Nitro-2-(piperidin-1-ylmethyl)quinoline was prepared using a similar experimental procedure as in Example 2, Step B by reacting 2-(bromomethyl)-6-nitroquinoline with piperidine. The desired compound was purified by column chromatography on silica gel, eluting with a gradient of 70% ethyl acetate in hexane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.70 (d, J = 8.7 Hz, 1H), 8.48 (d, J = 9.3 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 3.80 (s, 2H), 2.53 (m, 4H), 1.60 – 1.43 (m, 6H); ES-LCMS *m/z* 272 (M+H).



Step B: 2-(piperidin-1-ylmethyl)quinolin-6-amine

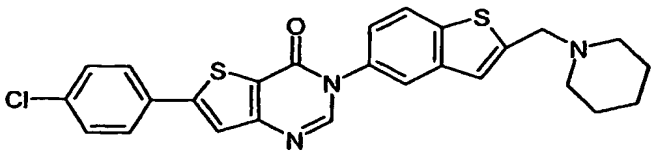
2-(Piperidin-1-ylmethyl)quinolin-6-amine was prepared using a similar experimental procedure as in Example 2, Step C by reducing 6-nitro-2-(piperidin-1-ylmethyl)quinoline with hydrogen gas and 10% Pd/C. The crude compound was used directly in the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.92 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 5.52 (brs, 2H) 3.60 (s, 2H), 2.54 (m, 4H), 1.56 – 1.41 (m, 6H); ES-LCMS *m/z* 242 (M+H).



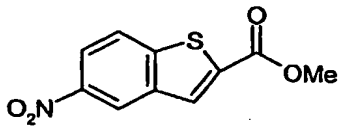
Step C: 6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-(piperidin-1-ylmethyl)quinolin-6-amine (Example 105, Step B). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.63 (d, J = 9.1 Hz, 1H), 8.36 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.07 (m, 5H), 7.65 (m, 2H), 3.50 (s, 2H), 2.53 (m, 4H), 1.86 – 1.49 (m, 6H); ES-LCMS *m/z* 487 (M+H).

Example 106



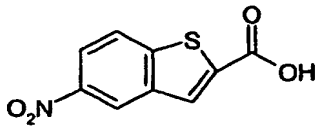
6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: methyl 5-nitro-1-benzothiophene-2-carboxylate

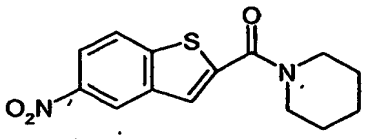
To a solution of 2-chloro-5-nitrobenzaldehyde 5.55 g (30 mmol) and methyl mercaptoacetate 2.68 mL (30 mmol) in DMF (60 mL) was added KOH (3.0 g) in 15 mL water dropwise. After stirring for 1 h the contents were poured into crushed ice and the solid filtered, washed with water and dried. The crude product was taken directly to the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ

8.96 (s, 1H), 8.40 (s,1H), 8.36 (s, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 3.90 (s, 3H); ES-LCMS *m/z* 238 (M+H).



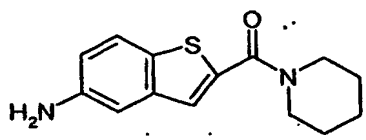
Step B: 5-nitro-1-benzothiophene-2-carboxylic acid

To a solution of methyl 5-nitro-1-benzothiophene-2-carboxylate 14.0 g (60 mmol) obtained in Step A in THF (60 mL) was added 60 mL of 1 N LiOH and the contents stirred for 16 h. After acidification, ethyl acetate (100 mL) was added and the organic layer separated. The organic layer was dried with $MgSO_4$ and then concentrated to afford the acid in quantitative yeild. ^1H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.40 (m,4H); ES-LCMS *m/z* 223 (M+H).



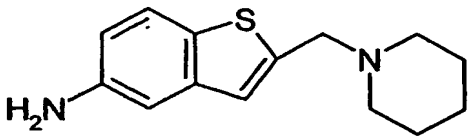
Step C: 1-[(5-nitro-1-benzothien-2-yl)carbonyl]piperidine

To a solution of 5-nitro-1-benzothiophene-2-carboxylic acid obtained in Step B (1.3 g, 5.83 mmol) in DCM (30 mL) was added Hunig's base 1.21 mL (6.99 mmol), EDC (1.23 g, 6.41 mmol), HOBT (6.99 mmol) and piperidine (0.633 mL, 6.41 mmol) and the contents stirred at room temperature for 16 h. After washing with satd. sodium chloride solution followed by satd. $NaHCO_3$ solution, the organic layer was dried with $MgSO_4$ and concentrated to afford the desired product. ^1H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 7.97 (s, 1H), 3.68 (m, 4H), 1.69 (m, 6H); ES-LCMS *m/z* 291 (M+H).



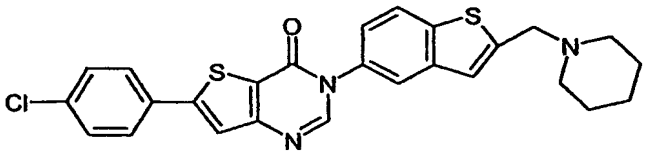
Step D: 2-(piperidin-1-ylcarbonyl)-1-benzothien-5-ylamine

To a solution of 1-[(5-nitro-1-benzothien-2-yl)carbonyl]piperidine (1.6 g, 5.80 mmol) in methanol (30 mL) was added 10% Pd/C (0.13 g) and the contents kept under H_2 at 40 psi. After 4 h, the solution was filtered through Celite and then concentrated under vacuum to afford the amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.63 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 6.83 (d, J = 8.6 Hz, 1H), 5.20 (brs, 2H), 3.36 (m, 4H), 1.68 (m, 6H); ES-LCMS *m/z* 261 (M+H).



Step E: 2-(piperidin-1-ylmethyl)-1-benzothiophen-5-amine

To a solution of 2-(piperidin-1-ylcarbonyl)-1-benzothien-5-ylamine (1.0 g, 3.85 mmol) in THF (20 mL) was added a 1.0 M solution of LAH in THF (19.2 mL, 19.2 mmol) and the contents refluxed for 20 h. After addition of 1 N sodium hydroxide, ethyl acetate was added and the organic layer separated. Drying ($MgSO_4$) and concentration afforded the desired product that was directly carried to the next step. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.50 (d, J = 8.6 Hz, 1H), 7.46 (s, 1H), 7.0 (s, 1H), 6.88 (d, J = 8.6 Hz, 1H), 5.02 (brs, 2H), 3.66 (s, 2H), 2.54 (m, 4H), 1.54 (m, 6H); ES-LCMS *m/z* 247 (M+H).

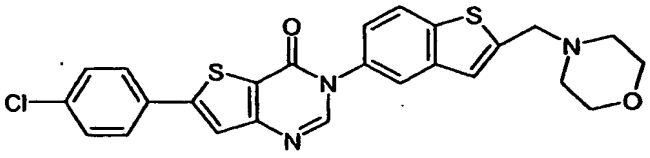


Step F: 6-(4-chlorophenyl)-3-[2-(piperidin-1-ylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

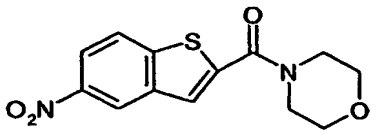
The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-

(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-(piperidin-1-ylmethyl)-1-benzothiophen-5-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.28 (m, 2H), 8.05 (m, 3H), 8.00 (d, J = 8.6 Hz, 1H), 7.82 (s, 1H), 7.64 (m, 2H), 3.81 (s, 2H), 2.48 (m, 4H), 1.65 (m, 6H); ES-LCMS *m/z* 492 (M+H).

Example 107

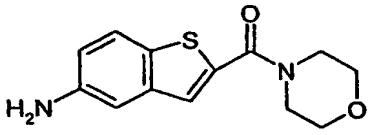


6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 4-[(5-nitro-1-benzothien-2-yl)carbonyl]morpholine

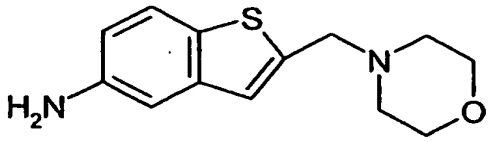
4-[(5-Nitro-1-benzothien-2-yl)carbonyl]morpholine was prepared using a similar experimental procedure as in Example 106, Step C by reacting 5-nitro-1-benzothiophene-2-carboxylic acid with morpholine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 3.67 (m, 8H); ES-LCMS *m/z* 293 (M+H).



Step B: 2-(morpholin-4-ylcarbonyl)-1-benzothien-5-ylamine

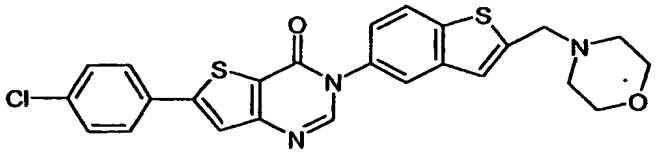
2-(Morpholin-4-ylcarbonyl)-1-benzothien-5-ylamine was prepared using a similar experimental procedure as in Example 106, Step D by reducing 4-[(5-nitro-1-benzothien-2-yl)carbonyl]morpholine with hydrogen gas and Pd/C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.47 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 6.83 (s,

1H), 6.63 (d, J = 8.4 Hz, 1H), 5.23 (brs, 2H), 3.34 (m, 8H); ES-LCMS *m/z* 263 (M+H).



Step C: 2-(morpholin-4-ylmethyl)-1-benzothiophen-5-amine

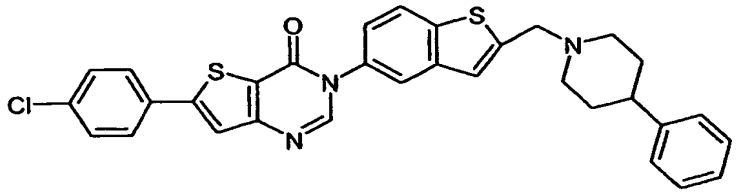
2-(Morpholin-4-ylmethyl)-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step E by reducing 2-(morpholin-4-ylcarbonyl)-1-benzothien-5-ylamine with LAH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 6.81 (s, 1H), 6.64 (d, J = 8.4 Hz, 1H), 5.0 (brs, 2H), 3.57 (t, J = 4.6 Hz, 4H), 2.49 (m, 4H); ES-LCMS *m/z* 249 (M+H).



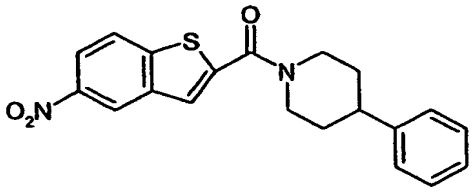
Step D: 6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D) by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-(morpholin-4-ylmethyl)-1-benzothiophen-5-amine (Example 107, Step C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.98 (m, 3H), 7.58 (d, J = 8.6 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.38 (s, 1H), 7.16 (m, 1H), 3.81 (s, 2H), 3.60 (m, 4H) 2.49 (m, 4H); ES-LCMS *m/z* 494 (M+H).

Example 108

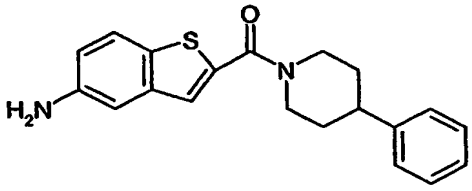


6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



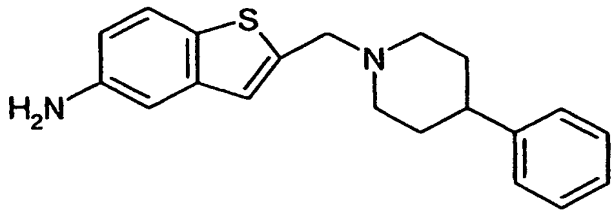
Step A: 1-[(5-nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperidine

1-[(5-Nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperidine was prepared using a similar experimental procedure as in Example 106, Step C by reacting 5-nitro-1-benzothiophene-2-carboxylic acid with 4-phenylpiperidine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.37 (d, J = 8.9 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.05 (s, 1H), 7.26 (m, 5H), 3.19 (m, 2H), 2.92 (m, 3H), 1.89 (m, 4H); ES-LCMS *m/z* 367 (M+H).



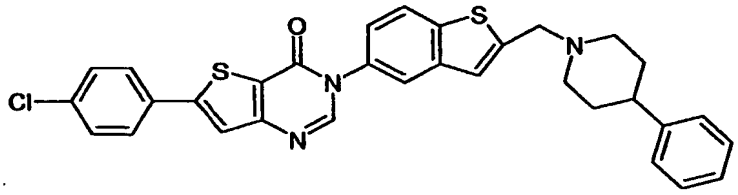
Step B: 2-[(4-phenylpiperidin-1-yl)carbonyl]-1-benzothiophen-5-amine

2-[(4-Phenylpiperidin-1-yl)carbonyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step D by reducing 1-[(5-nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperidine with hydrogen gas and Pd/C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.64 (d, J = 8.6 Hz, 1H), 7.48 (s, 1H), 7.35 (m, 5H), 7.02 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.21 (brs, 2H) 3.18 (m, 2H), 2.91 (m, 3H), 1.90 (m, 4H); ES-LCMS *m/z* 337 (M+H).



Step C: 2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothiophen-5-amine

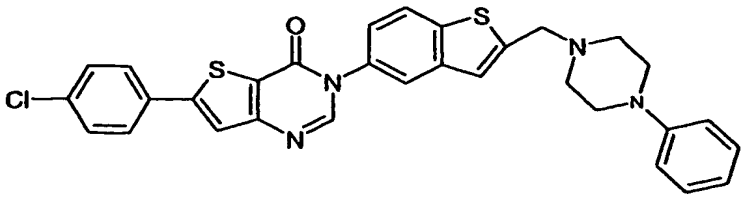
2-[(4-Phenylpiperidin-1-yl)methyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step E by reducing 2-[(4-phenylpiperidin-1-yl)carbonyl]-1-benzothiophen-5-amine with LAH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 8.5 Hz, 1H), 7.34 (m, 5H), 7.05 (s, 1H), 6.90 (s, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.03 (brs, 2H), 3.75 (s, 2H), 3.18 (m, 5H), 1.90 (m, 4H); ES-LCMS *m/z* 323 (M+H).



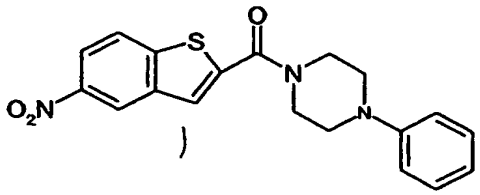
Step D: 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D) by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothiophen-5-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.04 (s, 1H), 7.99 (m, 3H), 7.64 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.35 (m, 6H), 3.90 (s, 2H), 3.09 (m, 5H), 1.91 (m, 4H); ES-LCMS *m/z* 568 (M+H).

Example 109

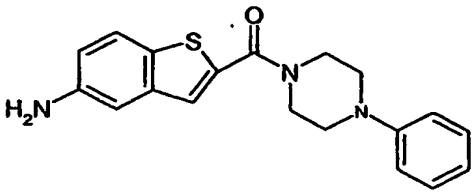


6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



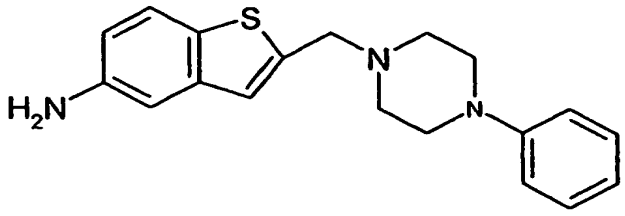
Step A: 1-[(5-nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperazine

1-[(5-Nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperazine was prepared using a similar experimental procedure as in Example 106, Step C by reacting 5-nitro-1-benzothiophene-2-carboxylic acid with 1-phenylpiperazine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.08 (s, 1H), 7.28 (m, 2H), 7.02 (m, 2H), 6.97 (m, 1H), 3.28 (m, 4H), 2.55 (m, 4H); ES-LCMS *m/z* 368 (M+H).



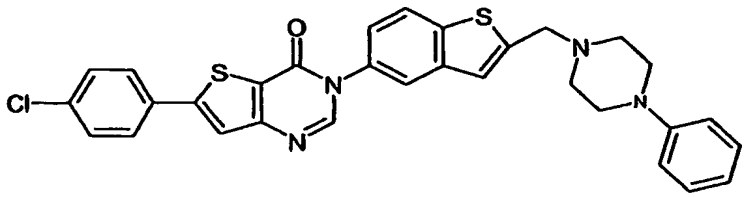
Step B: 2-[(4-phenylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine

2-[(4-Phenylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step D by reducing 1-[(5-nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperazine with hydrogen gas and Pd/C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.65 (d, J = 8.7 Hz, 1H), 7.52 (s, 1H), 7.30 (m, 2H), 7.03 (m, 3H), 6.86 (m, 2H), 5.25 (brs, 2H), 3.24 (m, 4H), 2.56 (m, 4H); ES-LCMS *m/z* 338 (M+H).



Step C: 2-[(4-Phenylpiperazin-1-yl)methyl]-1-benzothiophen-5-amine

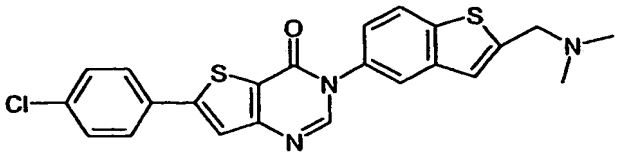
2-[(4-Phenylpiperazin-1-yl)methyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step E by reducing 2-[(4-phenylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine with LAH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (d, J = 8.6 Hz, 1H), 7.20 (m, 2H), 7.02 (s, 1H), 7.0 – 6.65 (m, 5H), 5.04 (brs, 2H), 3.78 (s, 2H), 3.24 (m, 4H), 2.54 (m, 4H); ES-LCMS *m/z* 323 (M+H).



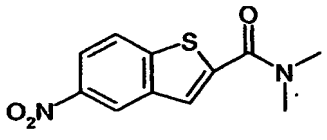
Step D: 6-(4-chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate (Example 1, Step D) with 2-[(4-phenylpiperazin-1-yl)methyl]-1-benzothiophen-5-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 7.99 (m, 6H), 7.64 (d, J = 8.5 Hz, 1H), 7.51 (m, 1H), 7.39 (s, 1H), 7.27 (m, 1H), 6.98 – 6.81 (m, 2H), 3.93 (s, 2H), 3.24 (m, 4H), 2.54 (m, 4H); ES-LCMS *m/z* 569 (M+H).

Example 110

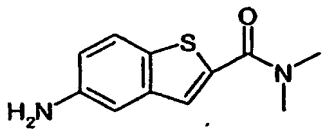


6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



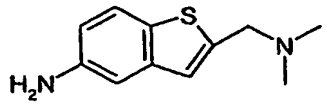
Step A: *N,N*-dimethyl-5-nitro-1-benzothiophene-2-carboxamide

N,N-Dimethyl-5-nitro-1-benzothiophene-2-carboxamide was prepared using a similar experimental procedure as in Example 106, Step C by reacting 5-nitro-1-benzothiophene-2-carboxylic acid with N,N-dimethylamine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.35 (d, J = 8.9 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.10 (s, 1H), 3.29 (s, 3H), 3.10 (s, 3H); ES-LCMS *m/z* 251 (M+H).



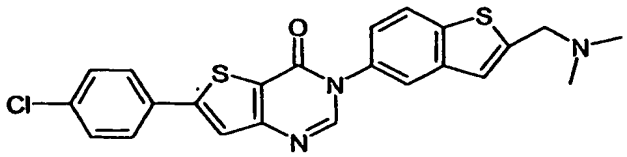
Step B: 5-amino-*N,N*-dimethyl-1-benzothiophene-2-carboxamide

5-Amino-*N,N*-dimethyl-1-benzothiophene-2-carboxamide was prepared using a similar experimental procedure as in Example 106, Step D by reducing *N,N*-dimethyl-5-nitro-1-benzothiophene-2-carboxamide with hydrogen gas and Pd/C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.63 (d, J = 8.7 Hz, 1H), 7.53 (s, 1H), 7.01 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.21 (brs, 2H), 3.21 (s, 6H); ES-LCMS *m/z* 221 (M+H).



Step C: 2-[(dimethylamino)methyl]-1-benzothiophen-5-amine

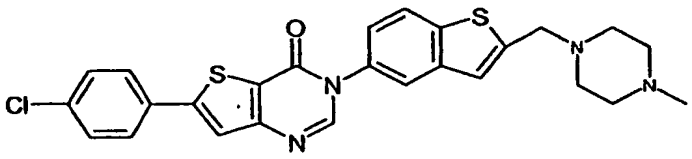
2-[(Dimethylamino)methyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step E by reducing 5-amino-*N*,*N*-dimethyl-1-benzothiophene-2-carboxamide with LAH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.53 (d, J = 8.6 Hz, 1H), 7.48 (s, 1H), 7.02 (s, 1H), 6.89 (d, J = 8.6 Hz, 1H), 5.03 (brs, 2H), 3.63 (s, 2H), 2.21 (s, 6H); ES-LCMS *m/z* 207 (M+H).



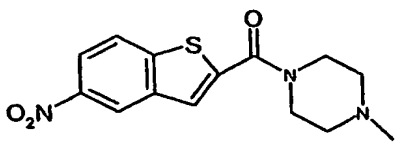
Step D: 6-(4-chlorophenyl)-3-{2-[(dimethylamino)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D) by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate with 2-[(dimethylamino)methyl]-1-benzothiophen-5-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.05 (m, 2H), 7.99 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H) 3.57 (s, 2H), 2.82 (s, 6H); ES-LCMS *m/z* 452 (M+H).

Example 111

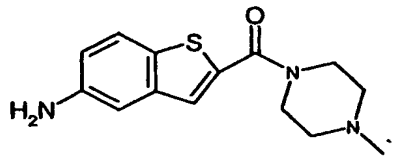


6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



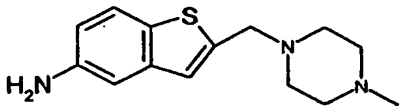
Step A: 1-methyl-4-[(5-nitro-1-benzothien-2-yl)carbonyl]piperazine

1-Methyl-4-[(5-nitro-1-benzothien-2-yl)carbonyl]piperazine was prepared using a similar experimental procedure as in Example 106, Step C by reacting 5-nitro-1-benzothiophene-2-carboxylic acid with N-methylpiperazine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 3.72 (m, 4H), 2.47 (m, 4H), 2.25 (s, 3H); ES-LCMS *m/z* 306 (M+H).



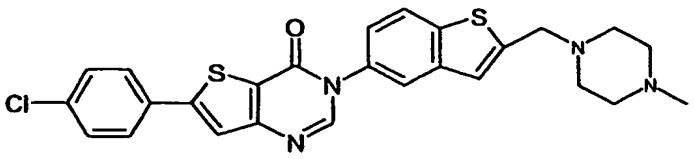
Step B: 2-[(4-methylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine

2-[(4-Methylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step D by reducing 1-methyl-4-[(5-nitro-1-benzothien-2-yl)carbonyl]piperazine with hydrogen gas and Pd/C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.63 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.01 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.23 (brs, 2H), 3.69 (t, J = 4.7 Hz, 4H), 2.41 (t, J = 4.8 Hz, 4H), 2.12 (s, 3H); ES-LCMS *m/z* 276 (M+H).



Step C: 2-[(4-methylpiperazin-1-yl)methyl]-1-benzothiophen-5-amine

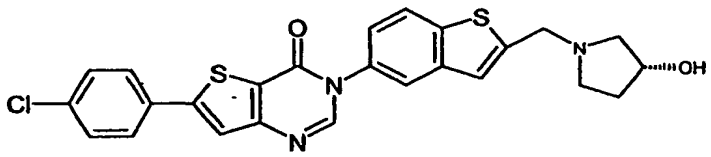
2-[(4-Methylpiperazin-1-yl)methyl]-1-benzothiophen-5-amine was prepared using a similar experimental procedure as in Example 106, Step E by reducing 2-[(4-methylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine with LAH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.02 (s, 1H), 6.86 (d, J = 8.7 Hz, 1H), 5.0 (brs, 2H), 3. 78 (s, 2H), 2.42 (m, 4H), 2.40 (m, 4H), 2.14 (s, 3H); ES-LCMS *m/z* 262 (M+H).



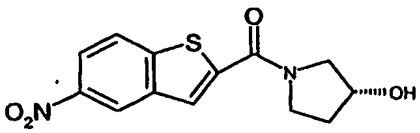
Step D: 6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D) by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate with 2-[(4-methylpiperazin-1-yl)methyl]-1-benzothiophen-5-amine. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.93 (m, 3H), 7.58 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6, Hz, 1H), 7.36 (s, 1H), 3.79 (s, 2H), 2.41 – 2.22 (m, 8H), 2.14 (s, 3H); ES-LCMS *m/z* 507 (M+H).

Example 112



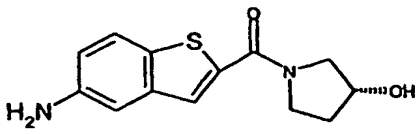
6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidin-1-yl]methyl}-1-benzothien-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: (3*R*)-1-[(5-nitro-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol

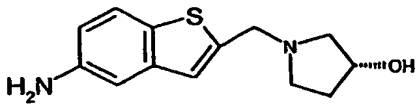
(3*R*)-1-[(5-Nitro-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol was prepared using a similar experimental procedure as in Example 106, Step C by reacting 5-nitro-1-benzothiophene-2-carboxylic acid with (3*R*)-pyrrolidin-3-ol. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 4.23 (m, 1H), 3.94 (brs, 1H), 3.61 – 3.33 (m, 4H), 1.89

(m, 2H); ES-LCMS *m/z* 293 (M+H).



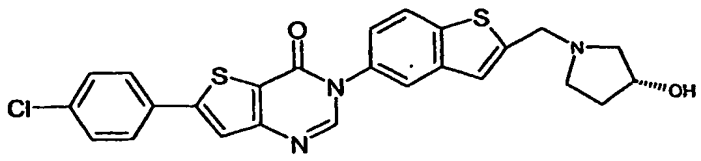
Step B: (3*R*)-1-[(5-amino-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol

(3*R*)-1-[(5-Amino-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol was prepared using a similar experimental procedure as in Example 106, Step D by reducing (3*R*)-1-[(5-nitro-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol with hydrogen gas and Pd/C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.01 (s, 1H), 6.82 (d, J = 8.7 Hz, 1H), 5.23 (brs, 2H), 4.21 (m, 1H), 3.96 (brs, 1H), 3.63 – 3.31 (m, 4H), 1.90 (m, 2H); ES-LCMS 263 *m/z* (M+H).



Step C: (3*R*)-1-[(5-amino-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol

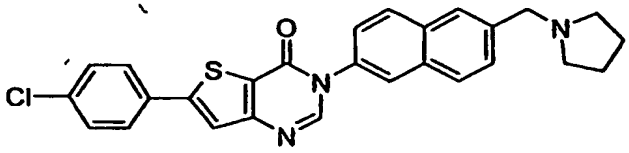
(3*R*)-1-[(5-Amino-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol was prepared using a similar experimental procedure as in Example 106, Step E by reducing 2-[(4-methylpiperazin-1-yl)carbonyl]-1-benzothiophen-5-amine with LAH. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.43 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.82 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.01 (brs, 2H), 4.61 (brs, 1H), 4.23 (m, 1H), 3.77 (s, 2H), 2.65 (m, 2H), 2.31 (m, 2H), 1.98 (m, 1H), 1.45 (m, 1H); ES-LCMS *m/z* 249 (M+H).



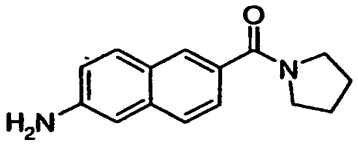
Step D: 6-(4-chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidin-1-yl]methyl}-1-benzothien-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The title compound was prepared using a similar experimental procedure as in Example 2, Step D) by reacting 5-(4-chlorophenyl)-3-{[(1E)-(dimethylamino)methylidene] amino}thiophene-2-carboxylate with (3*R*)-1-[(5-amino-1-benzothien-2-yl)carbonyl]pyrrolidin-3-ol. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.99 (s, 1H), 7.93 (m, 3H), 7.58 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.6 Hz, 1H), 7.35 (s, 1H), 4.73 (brs, 1H), 4.21 (m, 1H), 3.90 (s, 2H), 2.81 - 48 (m, 3H), 2.41 (m, 1H), 1.98 (m, 1H), 1.48 (m, 1H); ES-LCMS *m/z* 494(M+H).

Example 113



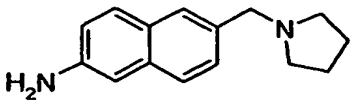
6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 6-(pyrrolidin-1-ylcarbonyl)naphthalen-2-amine

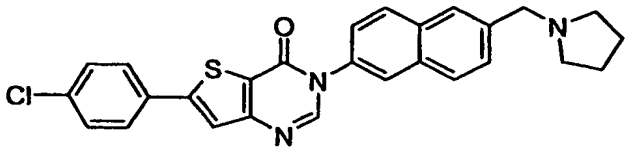
To a DMF solution (100 mL) containing 6-amino-2-naphthoic acid (5 g, 26.71 mmol, 1.0 eq) was added N,N-diisopropylethylamine (5.58 mL, 32.05 mmol, 1.2 eq) followed by HATU (15.2 g, 40.07 mmol, 1.5 eq). The resulting solution was stirred at room temperature for 20 min. To this stirring solution was added pyrrolidine (2.7 mL, 32.05 mmol, 1.2 eq). The resulting solution was stirred at room temperature for 18 h and quenched with a sat. $NaHCO_3$ solution (ca 20 mL). The cloudy solution was then poured into H_2O (ca 100 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were washed with H_2O (2x) and brine (1x); dried over $MgSO_4$ and concentrated *in vacuo*. The resulting off-white solid (4.57 g, 19.02 mmol,

71%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.61 (m, 2H), 6.92 (s, 2H), 3.93 (bs, 2H), 3.71 (m, 2H), 3.56 (m, 2H), 2.03 (m, 4H).



Step B: 6-(pyrrolidin-1-ylmethyl)naphthalen-2-amine

A solution of the intermediate from Example 113, Step A (4.57 g, 19.02 mmol, 1.0 eq) in anhydrous THF (100 mL) was slowly added to a cooled (0 °C) suspension of lithium aluminum hydride (1.8 g, 47.55 mmol, 2.5 eq) in anhydrous THF (200 mL). The resulting mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched by the sequential addition of H_2O (1.8 mL), 15% NaOH (1.8 mL), and H_2O (5.4 mL). The resulting precipitate was filtered and washed with THF. The filtrate was concentrated *in vacuo* and the resulting solid (4.3 g, 19.02 mmol, 100%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 3H), 7.39 (dd, J = 8.4, 1.6 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.95 (dd, J = 8.6, 2.2 Hz, 1H), 3.83 (bs, 2H), 3.73 (s, 2H), 2.59 (m, 4H), 1.82 (m, 4H).

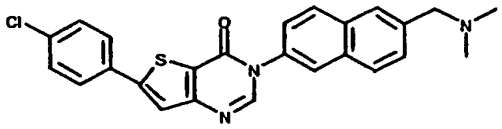


Step C: 6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one

To a dichloroethane solution (80 mL) containing the intermediate compound produced in Example 113, Step B (11.8 g, 52.21 mmol, 1.3 eq) and methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (12.93 g, 40.16 mmol, 1.0 eq, as described above) was added drop-wise a solution of $AlMe_3$ in hexanes (60.24 mL, 120.48 mmol, 3.0 eq). The resulting mixture was heated to reflux for 3 h, then cooled to room

temperature and placed in an ice bath. Formic acid (200 mL) was added very slowly and the resulting mixture heated to reflux for 4 h. Upon cooling to room temperature, the aqueous phase was made basic by the addition of a 50% NaOH solution. The organic phase was separated and the aqueous phase extracted (2x) with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was triturated with a small amount of CH_2Cl_2 to purify the title compound (13.4 g, 28.38 mmol, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.85 (m, 3H), 7.68 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.55 (s, 1H), 7.53 (dd, J = 8.6, 1.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 3.81 (s, 2H), 2.56 (m, 4H), 1.82 (m, 4H). AP-LCMS *m/z* 473 (M+H).

Example 114

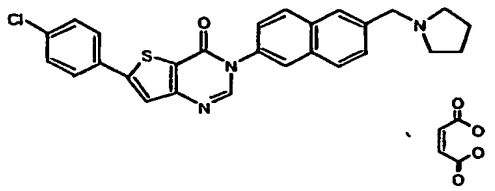


6-(4-chlorophenyl)-3-{6-[(dimethylamino)methyl]-2-naphthalenyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

A solution of $AlMe_3$ in hexanes (0.38 mL, 0.75 mmol) was added slowly to a solution of [(6-amino-2-naphthalenyl)methyl]dimethylamine (0.10 g, 0.50 mmol) and methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 0.16 g, 0.50 mmol) in dichloroethane (5 mL) at room temperature under N_2. After 5 minutes, the solution was heated to reflux for 2 h then cooled to room temperature. Formic acid (3 mL) was added carefully and the mixture was heated to reflux for 6 h. Upon cooling to room temperature, an aqueous 1N NaOH solution was added until the pH of the aqueous phase is alkaline, then added CH_2Cl_2 (250 mL) and water (100 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give the title compound as a white solid (0.20 g) with ca. 80% purity. The solid was partially dissolved in hot $CHCl_3$ (20 mL), filtered, and concentrated. The resulting solid was dissolved in $CHCl_3$ (15 mL) and then Et_2O (25 mL) was

added which produced a white precipitate. The solid was filtered and dried under vacuum to give the title compound as a white powder (0.089 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.89 – 7.84 (m, 3H), 7.68 (d, J = 8.4 Hz, 2H), 7.61 – 7.52 (m, 3H), 7.45 (d, J = 8.5 Hz, 2H), 3.64 (s, 2H), 2.32 (s, 6H). EI-LCMS *m/z* 446 (M+H).

Example 115

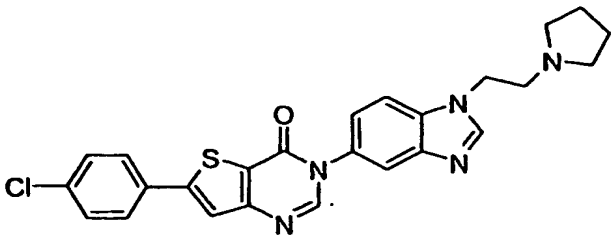


6-(4-chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt

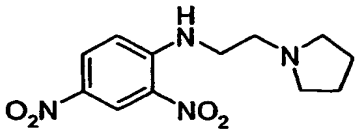
A solution of $AlMe_3$ in hexanes (5.36 mL, 10.71 mmol) was added slowly to a solution of [6-(1-pyrrolidinylmethyl)-2-naphthalenyl]amine (1.05 g, 4.65 mmol) and methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (Example 1, Step D; 1.15 g, 3.57 mmol) in dichloroethane (40 mL) at room temperature under N_2. After 5 minutes, the solution was heated to reflux for 3 h then cooled to room temperature. Formic acid (25 mL) was added carefully and the mixture was heated to reflux for 4 h. Upon cooling to room temperature, an aqueous 1 N NaOH solution was added until the pH of the aqueous phase is alkaline. Extracted with CH_2Cl_2 (2 x 250 mL) and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. The solid was purified by column chromatography through silica gel eluting with an increasing gradient from ethyl acetate to 10% MeOH/ethyl acetate to give the title compound in ca. 75% purity. The solid was dissolved in hot DMSO, cooled to room temperature and filtered. The resulting solid (1.1 g) was partially dissolved in $CHCl_3$ and maleic acid (1 equivalent) was added. The solution was filtered and concentrated to give the title compound as the maleate salt (0.89 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.58 (s, 1H), 8.22 – 8.11 (m, 4H), 8.04 (s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.78 – 7.73 (m, 2H), 7.60 (d, J = 8.6 Hz, 2H), 6.03 (s, 2H), 4.56

(s, 4H), 3.35 – 3.10 (m, 4H), 2.11 – 1.84 (m, 4H). EI-LCMS *m/z* 472 (M+H).

Example 116

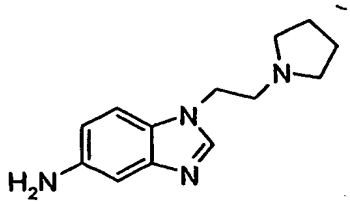


6-(4-chlorophenyl)-3-{1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: (2,4-Dinitrophenyl)[2-(1-pyrrolidinyl)ethyl]amine

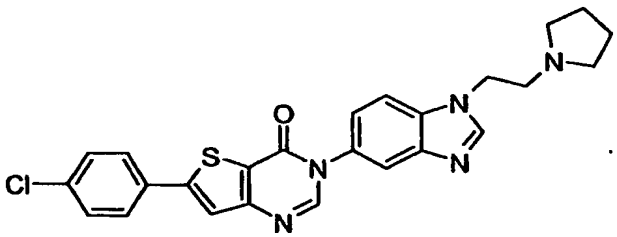
2, 4-Dinitrofluorobenzene (18.6 g, 0.10 mol) was added to a stirring THF (150 mL) solution of [2-(1-pyrrolidinyl)ethyl]amine (11.40g, 0.10mol) and triethylamine (10.19 g, 0.10 mol). After stirring at ambient temperature for 2 hours the reaction was diluted with sodium hydroxide (20 mL, 5 N), diluted with ethyl acetate and extracted twice with brine, once with water, dried, filtered and concentrated to give a yellow powder (28.0 g, 100%). LCMS m/z 281 (MH+). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (m, 1H), 8.80 (s, 1H), 8.22 (d, 1H), 7.20 (d, 1H), 3.56 (m, 2H), 2.77 (t, 2H), 2.55 (m, 4H), 1.70 (m, 4H).



Step B: 1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-5-amine

A dioxane (200 mL) solution of (2,4-dinitrophenyl)[2-(1-pyrrolidinyl)-ethyl]amine (28.0 g, 0.10 mol) with $Pd(OH)_2/C$ (2.0 g) was agitated on a Parr

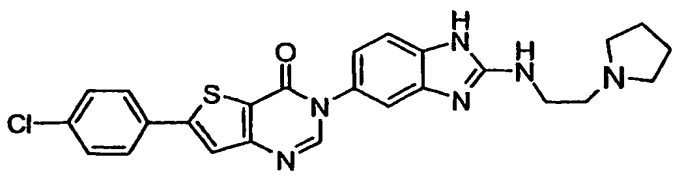
shaker apparatus under 45 psi hydrogen pressure for 3 hours. The reaction mixture was removed to a nitrogen atmosphere, filtered through celite and combined with triethylorthoformate (100 mL) and HCl/dioxane (20 mL, 4 M). After warming to reflux overnight, the reaction was concentrated, mixed with aqueous sodium hydroxide (20 mL, 5 N), extracted with ethyl acetate, concentrated and chromatographed using EtOH:EtOAc/1:1 on silica gel to give a deep tan solid (20 g, 87%). LCMS m/z 231 (MH+). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.20 (s, 1H), 8.00 (d, 1H), 7.51 (d, 1H), 4.70 (m, 2H), 4.35 (t, 2H), 2.77 (t, 2H), 2.55 (m, 4H), 1.64 (m, 4H).



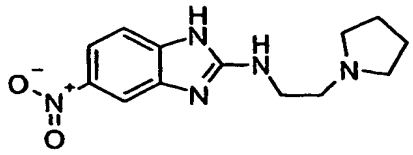
Step C: 6-(4-chlorophenyl)-3-{1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one

An ethanol (10 mL) solution of 1-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimida-zol-5-amine (0.46 g, 0.002 M) and methyl 5-(4-chlorophenyl)-3-{[(1*Z*)-(dimethylamino)methylidene]-amino}-2-thiophenecarboxylate (Example 1, Step D; 0.319 g, 0.001 mol) was warmed to reflux overnight, then filtered at ambient temperature to give a tan solid (0.155 g, 32%). LCMS m/z 476 (MH+). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.40 (s, 1H), 8.03 (s, 1H), 7.97 (d, 2H), 7.84 (s, 1H), 7.80 (d, 1H), 7.62 (d, 2H), 7.40 (d, 1H), 4.44 (t, 2H), 2.84 (t, 2H), 2.42-2.58 (m, 4H), 1.64 (m, 4H).

Example 117

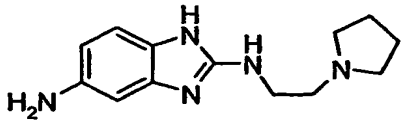


6-(4-chlorophenyl)-3-(2-{[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 5-nitro-*N*-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-2-amine

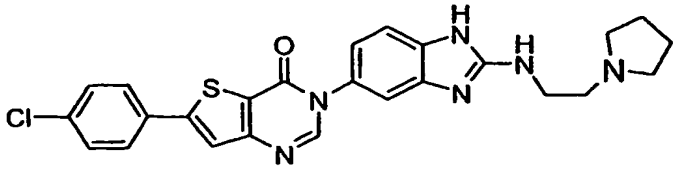
A solution of 2-chloro-5-nitro-1*H*-benzimidazole (1.0 g, 5.06 mmol) in 20 mL ethanol was treated with [2-(1-pyrrolidinyl)ethyl]amine (835 µL, 6.6 mmol) and heated to reflux for 1 hour. More [2-(1-pyrrolidinyl)ethyl]amine (1670 µL, 13.2 mmol) was added and the reaction was placed in a sealed tube at 160 °C overnight. The reaction was concentrated to produce an oil that was a mixture of the 5-nitro-*N*-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-2-amine and [2-(1-pyrrolidinyl)ethyl]amine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.7 (m, 4 H) 2.4 (m, 4 H) 2.5 (m, 2 H) 2.6 (t, *J*=6.6 Hz, 2 H) 7.2 (d, *J*=8.8 Hz, 1 H) 7.9 (dd, *J*=8.8, 2.4 Hz, 1 H) 7.9 (d, *J*=2.4 Hz, 1 H). ES-LCMS *m/z* 276 (M+H).



Step B: N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,5-diamine

The mixture of 5-nitro-*N*-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazol-2-amine and [2-(1-pyrrolidinyl)ethyl]amine obtained in the previous reaction was dissolved in 30 mL ethanol, treated with 10% palladium on carbon (500 mg, 0.46 mmol), and hydrogenated on a Parr apparatus at 30 psi. When hydrogen uptake was complete, the reaction was filtered through a plug of silica/celite and concentrated in vacuo. Chromatography on 12 g silica with 0-10% 2M ammonia in methanol/dichloromethane produced N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,5-diamine along with [2-(1-pyrrolidinyl)ethyl]amine (800 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.7 (m, 4 H) 2.4 (m, 2 H) 2.5 (t, *J*=6.4

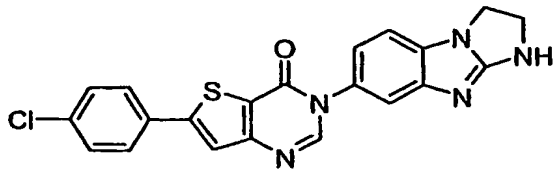
Hz, 2 H) 2.6 (t, *J*=6.6 Hz, 2 H) 2.8 (t, *J*=6.2 Hz, 2 H) 6.2 (dd, *J*=8.1, 2.0 Hz, 1 H) 6.4 (d, *J*=1.8 Hz, 1 H) 6.8 (d, *J*=8.2 Hz, 1 H)



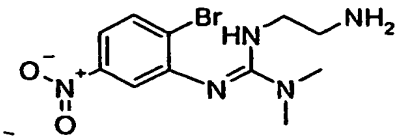
Step C: 6-(4-chlorophenyl)-3-(2-{[2-(1-pyrrolidinyl)ethyl]amino}-1*H*-benzimidazol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The mixture of N^2-[2-(1-pyrrolidinyl)ethyl]-1*H*-benzimidazole-2,5-diamine and [2-(1-pyrrolidinyl)ethyl]amine obtained in the previous reaction, was treated with methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (1.05 g, 3.26 mmol) and heated in 5 g phenol at 170 °C for 2 hours. The reaction was directly chromatographed on 40 g silica with 0-10% 2 M ammonia in methanol/dichloromethane to provide the desired product (449 mg). The byproduct 6-(4-chlorophenyl)-3-[2-(1-pyrrolidinyl)ethyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (139 mg) was also isolated. ^{1}H NMR (400 MHz DMSO-d_6) δ 1.7 (m, 4 H) 2.5 (m, 4 H) 2.6 (t, *J*=6.6, 6.2 Hz, 2 H) 3.4 (m, 2 H) 6.7 (t, *J*=5.9 Hz, 1 H) 6.9 (dd, *J*=8.2, 2.0 Hz, 1 H) 7.2 (d, *J*=8.2 Hz, 1 H) 7.2 (d, *J*=2.2 Hz, 1 H) 7.6 (d, *J*=8.8 Hz, 2 H) 7.9 (d, *J*=8.8 Hz, 2 H) 8.0 (m, 1 H) 8.4 (m, 1 H). ES-LCMS *m/z* 491 (M+H).

Example 118

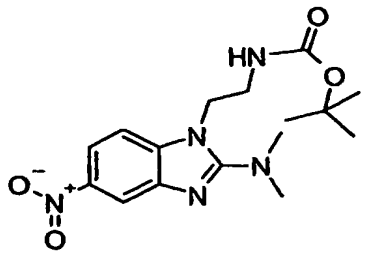


6-(4-chlorophenyl)-3-(2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one



Step A: 1,1-dimethylethyl (2-{[[(2-bromo-5-nitrophenyl)amino](dimethylamino)methylidene]amino}ethyl)carbamate

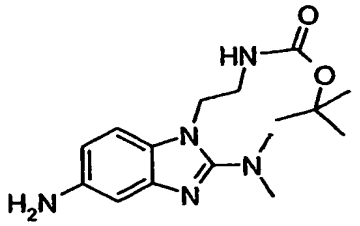
A solution of *N'*-(2-bromo-5-nitrophenyl)-*N*,*N*-dimethylcarbamimidic chloride (1.64 mmol) in 20 mL dichloromethane was treated with triethylamine (1.14 mL, 8.2 mmol) and 1,1-dimethylethyl (2-aminoethyl)carbamate (395 mg, 2.46 mmol) and stirred for 36 hours. No reaction had occurred. The dichloromethane was removed by distillation and replaced with 10 mL tetrahydrofuran and the reaction was heated to reflux overnight. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.3 (s, 9 H) 2.7 (s, 6 H) 2.9 (m, 2 H) 3.6 (m, 1 H) 7.3 (m, 2 H) 7.7 (d, *J*=9.0 Hz, 1 H).



Step B: 1,1-dimethylethyl {2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethyl}carbamate

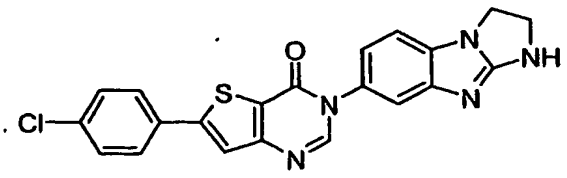
A solution of 1,1-dimethylethyl (2-{[[(2-bromo-5-nitrophenyl)amino](dimethylamino)methylidene]amino}ethyl)carbamate (1.64 mmol), BINAP (92 mg, 0.15 mmol) and cesium carbonate (746 mg, 2.3 mmol) in 16 mL tetrahydrofuran was treated with palladium acetate (22 mg, 0.1 mmol) and heated to reflux for 24 hours. More BINAP and palladium acetate were added and the reaction refluxed for an additional 24 hours. The reaction was diluted with 1 N sodium hydroxide and extracted with dichloromethane. The organics were dried over magnesium sulfate, concentrated in vacuo and the residue chromatographed on 12 g silica with 0-10% methanol/dichloromethane to produce the desired product contaminated with

BINAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (s, 9 H) 3.0 (s, 6 H) 3.4 (dt, *J*=6.2 Hz, 2 H) 4.2 (t, *J*=6.4 Hz, 2 H) 5.0 (t, *J*=5.7 Hz, 1 H) 7.2 (d, *J*=8.8 Hz, 1 H) 8.0 (dd, *J*=8.8, 2.0 Hz, 1 H) 8.3 (d, *J*=2.0 Hz, 1 H).



Step C: 1,1-dimethylethyl {2-[5-amino-2-(dimethylamino)-1*H*-benzimidazol-1-yl]ethyl}carbamate

The mixture of 1,1-dimethylethyl {2-[2-(dimethylamino)-5-nitro-1*H*-benzimidazol-1-yl]ethyl}carbamate and BINAP obtained in the previous reaction was dissolved in 20 mL ethanol, treated with 10% palladium on carbon (250 mg, 0.23 mmol), and hydrogenated on a Parr apparatus at 40 psi. When hydrogen uptake was complete, the reaction was filtered through a plug of silica/celite and concentrated in vacuo to produce the desire product contaminated with BINAP. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 (s, 9 H) 2.9 (s, 6 H) 3.4 (dt, *J*=7.0, 6.0, 5.3 Hz, 2 H) 4.1 (t, *J*=6.2 Hz, 2 H) 4.9 (t, *J*=4.9 Hz, 1 H) 6.5 (dd, *J*=8.2, 1.8 Hz, 1 H) 6.9 (d, *J*=1.6 Hz, 1 H) 7.0 (d, *J*=8.2 Hz, 1 H).



Step D: 6-(4-chlorophenyl)-3-(2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one

The mixture of 1,1-dimethylethyl {2-[5-amino-2-(dimethylamino)-1*H*-benzimidazol-1-yl]ethyl}carbamate and BINAP obtained in the previous reaction was treated with methyl 5-(4-chlorophenyl)-3-{[(*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (270 mg, 0.84

mmol) and heated in 1 g phenol at 200 °C for 1 hour. Upon cooling, the reaction was diluted with methanol, and the resulting precipitate was collected by filtration. This residue was dissolved in dimethylsulfoxide, treated with 4 N HCl in dioxane, and precipitated by addition of ethylacetate and diethylether to yield 139 mg of 6-(4-chlorophenyl)-3-(2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazol-7-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.5 (s, 1 H) 4.3 (m, 4 H) 7.4 (dd, *J*=8.4, 1.8 Hz, 1 H) 7.6 (m, 3 H) 7.6 (d, *J*=1.8 Hz, 1 H) 7.9 (d, *J*=8.6 Hz, 2 H) 8.0 (s, 1 H) 8.4 (s, 1 H) 9.5 (brs, 1 H). ES-LCMS *m/z* 420 (M+H).

The activity of the compounds used in this invention may be assessed in a functional assay of MCHR1 as follows:

Materials

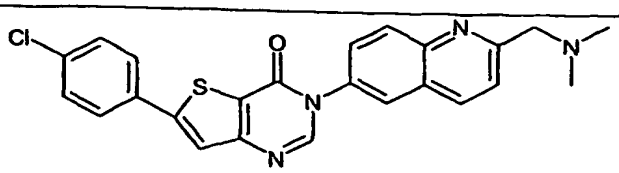
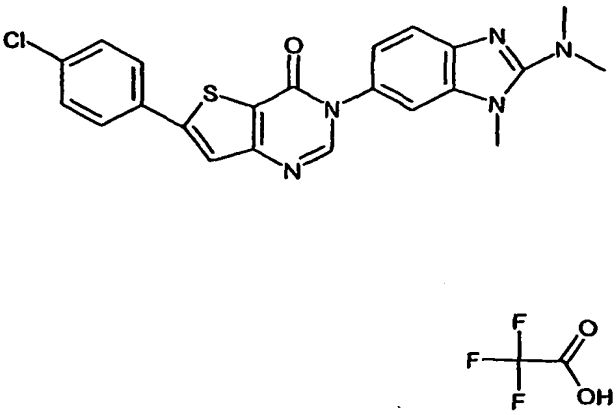
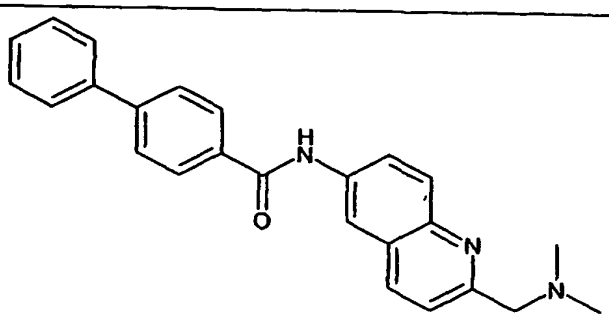
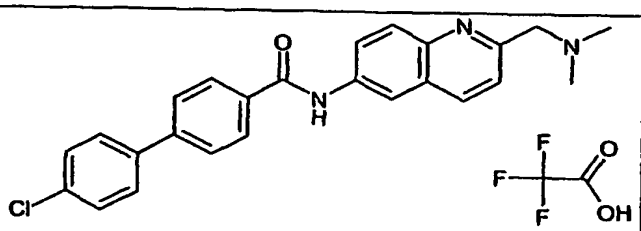
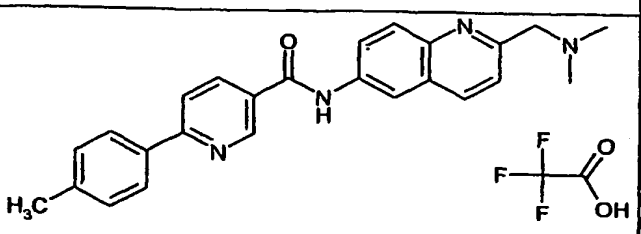
Black, 96-well, tissue culture-treated plates (#3904) were obtained from Corning Costar, (Cambridge, MA), LucPlus™ Luciferase Reporter Gene Assay Kit (# 6016969) was from Packard (Meriden, CT), plate seals (#097-05-00006) were from Beckman/Sagian (Fullerton, CA). DMEM/F12 medium (#11039-021), fetal bovine serum (# 16140-071), L-glutamine (#25030-081), 0.05% trypsin (# 25300-054), G418 (#10131-035) and dPBS (#4190-144) were obtained from Gibco BRL (Gaithersburg, MD). Thrombin (T7009) was obtained from Sigma Chemical Co (St. Louis, MO), MCH peptide (H-1482) was obtained from BaChem California (Torrance, CA). Chinese hamster ovary (CHO-K1) cells were obtained from the American Type Culture Collection (Rockville, MD).

Methods

CHO cells, stably expressing an elkgal4-luc$^+$ reporter gene (host) were transfected by electroporation with the human melanin-concentrating hormone one receptor. A stable clone was selected using G418 for functional antagonist assays. MCH1R-elkgal4-luc$^+$ CHO cells were propagated in complete medium (DMEM/F12, 5% FBS, 2 mM l-glutamine) in T225 flasks. Forty-eight hours prior to assay, cells were harvested with 2 mL of 0.05%

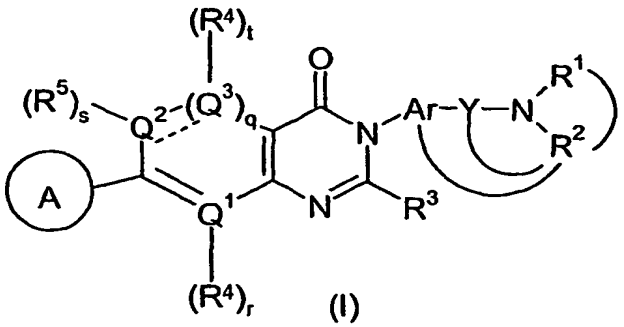
trypsin, washed with complete medium and plated at a concentration of 10,000 cells/well in complete medium in black 96-well plates. Eighteen hours prior to the assay, the medium was removed from the cells by aspiration and replaced with 90 µl/well of serum-free DMEM/F12. At the time of the assay, antagonists (1 µL, 100% DMSO) as 10-point concentration curves were pipetted into the medium and plates were incubated for forty-five minutes at 37°C in a cell culture incubator. Following this incubation. 10 uL of an EC_{80} concentration of MCH was added to the medium and plates were incubated for five hours at 37°C in a cell culture incubator. The medium was aspirated by vacuum followed by the addition of 50 µl of a 1:1 mixture of LucPlus™ and dPBS/1 mM $CaCl_2$/1 mM $MgCl_2$. The aspiration step was performed in order to avoid potential assay interference by compounds which could inhibit or stimulate luciferase activity or could inhibit light signal. Plates were sealed and subjected to dark adaptation at room temperature for 10 minutes before luciferase activity was quantitated on a TopCount™ microplate scintillation counter (Packard) using 3 seconds/well count time. The ability of the antagonist to inhibit the MCH EC_{80} response was quantified by non-linear regression analysis using a curve-fitting program based in Microsoft ExCel. Specificity of the MCHR1 response was determined using the same protocol by measuring the ability of said antagonists to inhibit an EC_{80} thrombin response (endogenous) in the host cells.

The compounds described in Examples have a pIC_{50} value of greater than 7. For example, the compounds of Examples 1 and 11 have the respective MCHR1 pIC_{50} values shown below. Also included are exemplified compounds from WO 01/82925A1 from Takeda. As can be seen from Table 2, the compounds claimed herein are over 10-fold more active than the cited examples from WO 01/82925A1.

Example	Structure	MCHR1 pIC_{50}
Example 1		9.1
Example 11		8.8
WO 01/82925A1 Example 15		6.3
WO 01/82925A1 Example 6 (trifluoracetic acid salt)		7.5
WO 01/82925A1 Example 17 (trifluoroacetic acid salt)		6.4

What is claimed is:

1. A compound of formula (I) comprising:



(I)

a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, wherein:

(A) is aryl or heteroaryl, optionally substituted one to four times by at least one substituent selected from the group consisting of C_{1-6} straight or branched alkyl, alkenyl, halo, amino, alkylamino, dialkylamino, hydroxy, C_{1-6} alkoxy, cyano, nitro, and alkylthio groups;

the dashed line connecting Q^2 to Q^3 represents an optional bond;

q, r, s, and t are each independently 0 or 1;

when q is 1, the dashed line is a bond;

Q^1 and Q^3 are each independently C or N;

when q is 0 then Q^2 is N, S, or O;

when q is 1, then Q^2 is C or N; when q is 1 and Q^2 is N, then s is 0;

when Q^2 is S or O, s is 0;

when Q^1 is N, r is 0;

when Q^3 is N, t is 0;

R^3 is selected from the group consisting of hydrogen, amino, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and C_{1-3} alkylthio;

when Q^1 or Q^3 is C, then each corresponding R^4 is independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

when q is 1 and Q^2 is C or when q is 0 and Q^2 is N, then R^5 is selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6}

cycloalkyl, C_{1-6} alkoxy, amino, alkylamino, dialkylamino, hydroxy, cyano, alkylthio, and halo;

Ar is an optionally substituted fused bicyclic ring;

Y is a bond or a C_{1-6} alkylene, optionally substituted;

(i) R^1 and R^2 are each independently selected from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, and a 5- or 6-membered heterocycle wherein said alkyl, said cycloalkyl, and said heterocycle are optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, oxo, alkoxy and halo;

or (ii) R^1 and R^2 are each selected from the group consisting of aryl and a 5- or 6-membered heteroaryl containing 1, 2, or 3 heteroatoms selected from N, O, and S, wherein said aryl and said heteroaryl are optionally substituted 1, 2, or 3 times with at least one substituent selected from halo, C_{1-6} straight or branched alkyl, C_{3-6} cycloalkyl, C_{1-6} alkenyl, C_{3-6} cycloalkenyl, hydroxy, C_{1-6} alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, and phenyl;

or (iii) R^1 and R^2 together with the nitrogen atom to which they are bonded form a 4-8 membered heterocyclic ring or a 7-11 membered bicyclic heterocyclic ring, wherein said 4-8 membered heterocyclic ring and said 7-11 membered bicyclic heterocyclic ring contain 1, 2 or 3 heteroatoms selected from the group consisting of N, O, and S, and wherein either said heterocyclic ring or said bicyclic heterocyclic ring is optionally substituted one to four times by at least one substituent selected from the group consisting of by phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, or halo;

or (iv) R^2 together with the adjacent nitrogen atom and Y may form an optionally substitued nitrogen-containing heterocycle, or R^2 together with the adjacent nitrogen atom, Y, and Ar may form an optionally substituted nitrogen-containing heterocycle or salt thereof, wherein said heterocycle is optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy, oxo, amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, and halo.

2. The compound according to Claim 1 wherein said Ⓐ is an aryl substituted with at least one substituent selected from the group consisting of halo, C_{1-3} alkyl, and C_{1-3} alkoxy.

3. The compound according to Claim 2 wherein Ⓐ is an aryl substituted with a group selected from the group consisting of fluoro, chloro, and methoxy.

4. The compound according to Claim 1 wherein said Ⓐ is a halo-substituted aryl or a halo-substituted heteroaryl; q is 0; s is 0; Q^1 is C; Q^2 is S; and R^4 is hydrogen or halo.

5. The compound according to Claim 4 wherein Ⓐ is 4-chlorophenyl; and R^3 and R^4 are each hydrogen.

6. The compound according to Claim 1 wherein Q^1, Q^2, and Q^3 are each C; and q, r, s, and t are 1.

7. The compound according to Claim 1 wherein Q^1 is N; Q^2 is S; and q, r, s, and t are 0.

8. The compound according to Claim 1 wherein R^3 is hydrogen or C_{1-3} alkyl.

9. The compound according to Claim 8 wherein R^3 is hydrogen or methyl.

10. The compound according to Claim 1 wherein Ar is a 9-14 membered fused polycyclic aromatic ring or a 9-14 membered fused polycyclic heteroaromatic ring.

11. The compound of Claim 10 wherein the fused polycyclic aromatic ring or the fused polycyclic heteroaromatic ring is a ten-membered ring.

12. The compound of Claim 11 wherein said fused polycyclic aromatic ring is naphthalene or the fused polycyclic heteroaromatic ring is quinoline.

13. The compound of Claim 11 wherein Y is an optionally substituted C_{1-6} alkylene.

14. The compound of Claim 13 wherein Y is a C_{1-3} alkylene, optionally substituted.

15. The compound of Claim 14 wherein Y is methylene.

16. The compound according to Claim 1 wherein in (i), R^1 and R^2 are each selected independently from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} alkyl.

17. The compound according to Claim 16 wherein in (i), R^1 and R^2 are selected independently from the group consisting of hydrogen, C_{1-3} straight or branched alkyl, and C_{3-6} alkyl.

18. The compound according to Claim 1 wherein, in (ii), either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is hydrogen, C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

19. The compound according to Claim 1 wherein, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicyclic heterocyclic ring; having 1 or 2 heteroatoms selected from the group N, O, and S; wherein said heterocyclic ring and said bicyclic heterocyclic ring are optionally

substituted up to two times with a substituent selected from the group consisting of oxo and halo.

20. The compound according to Claim 19 wherein R^1 and R^2 together with the nitrogen atom to which they are bonded form a heterocyclic ring selected from the group consisting of morpholine, piperidine, piperazine, pyrrolidine, 1,3-thiazolidine, 1H-imidazole, 4,5-dihydro-1H-imidazole, 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline; and wherein said heterocyclic ring is optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

21. The compound according to Claim 1 wherein, in (iv), Y is a C_{1-6} alkylene and R^2 is linked to said Y to form a 3 to 7-membered ring.

22. The compound according to Claim 21 wherein said ring is a 5 to 7-membered ring optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

23. The compound according Claim 1 wherein the compound is selected from the group consisting of

6-(4-chlorophenyl)-3-{6-[(4-hydroxy-1-piperidinyl)methyl]-2-naphthalenyl}thieno[3,2-d]pyrimidin-4(3H)-one;

6-(4-chlorophenyl)-3-[6-(pyrrolidin-1-ylmethyl)-2-naphthyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-d]pyrimidin-4(3H)-one;

6-(4-fluorophenyl)-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-fluorophenyl)-3-[2-(piperidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2-methyl-4,5-dihydro-1*H*-imidazol-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

6-(4-chlorophenyl)-3-{2-[(2,2,6,6-tetramethylpiperidin-1-yl)methyl]quinolin-6-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one;

and 6-phenyl-3-[2-(pyrrolidin-1-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

24. The compound of Claim 10 wherein Ar is a 9-membered fused polycyclic heteroaromatic ring.

25. The compound of Claim 24 wherein Ar is benzimidazole, indole, benzothiophene, benzothiazole, or benzofuran.

26. The compound of Claim 25 wherein Y is a bond or C_{1-3} alkylene.

27. The compound of Claim 26 wherein Y is a bond or methylene.

28. The compound according to Claim 24 wherein, in (i), R^1 and R^2 are each selected independently from the group consisting of hydrogen, C_{1-6} straight or branched alkyl, and C_{3-6} alkyl.

29. The compound according to Claim 28 wherein, in (i), R^1 and R^2 each are selected independently from the group consisting of hydrogen, C_{1-3} straight or branched alkyl, and C_{3-6} alkyl.

30. The compound according to Claim 24 wherein, in (ii), either R^1 or R^2 is aryl or heteroaryl, the other remaining R^1 or R^2 is hydrogen, C_{1-6} alkyl, or a C_{3-6} cycloalkyl.

31. The compound according to Claim 24 wherein, in (iii), R^1 and R^2 together with the nitrogen atom to which they are bonded form a 5- or 6-membered heterocyclic ring or an 8- to 11-membered bicyclic heterocyclic ring having 1 or 2 heteroatoms selected from the group N, O, and S; and wherein said heterocyclic ring and said bicyclic heterocyclic ring may be optionally substituted up to two times with a substituent selected from the group consisting of oxo and halo.

32. The compound according to Claim 31 wherein said ring is selected from the group consisting of morpholine, piperidine, piperazine, pyrrolidine, 1,3-thiazolidine, 1H-imidazole, 4,5-dihydro-1H-imidazole, 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, or 1,2,3,4-tetrahydroisoquinoline; and wherein said heterocyclic ring is optionally substituted one to four times by at least one substituent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

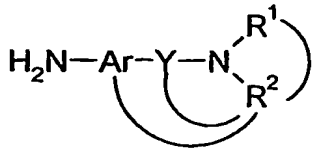
33. The compound according to Claim 24 wherein, in (iv), Y is a C_{1-6} alkylene and is linked to R^2 to form a 3-7 membered ring.

34. The compound according to Claim 33 wherein said 3-7 membered ring is a 5 to 7 membered ring optionally substituted one to four times by at least one substitutent selected from the group consisting of phenyl, C_{1-3} alkyl, hydroxy, alkoxy, oxo, and halo.

35. The compound according Claim 24 wherein the compound is

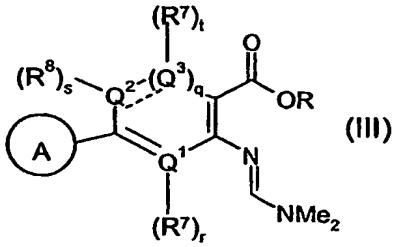
6-(4-chlorophenyl)-3-[2-(dimethylamino)-1-methyl-1*H*-benzimidazol-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one.

36. A process for preparing a compound of Claim 1 comprising reacting an aniline of formula (II)



(II)

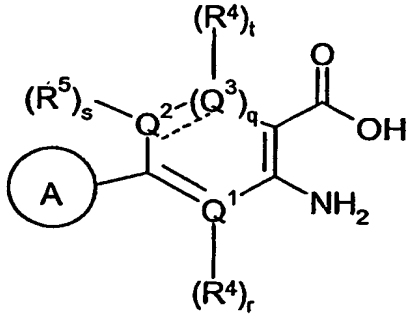
with a compound of formula (III)



(III)

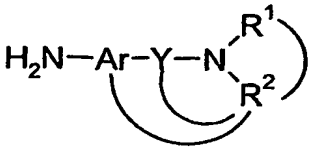
while heating in a solvent; wherein  , R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I); and R is C_1-C_4 alkyl.

37. A process for preparing a compound of Claim 1 comprising coupling an amino acid of formula (IV)



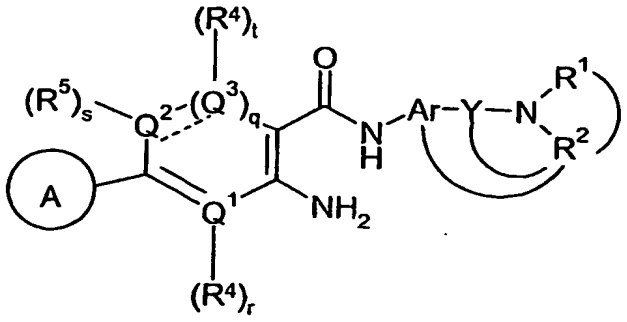
(IV)

with an aniline of formula (II)



(II)

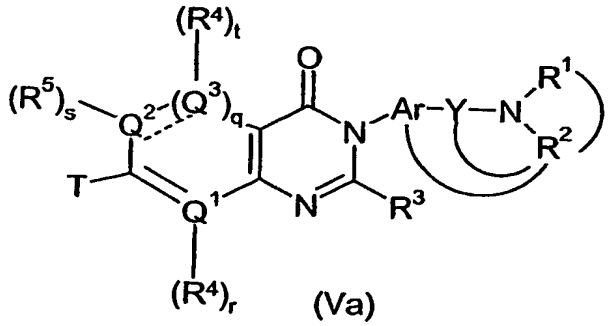
in a solvent in the presence of at least one coupling agent to produce a compound of formula (V)



(V)

and cyclizing said compound of formula (V) to form a compound of formula (I) and wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

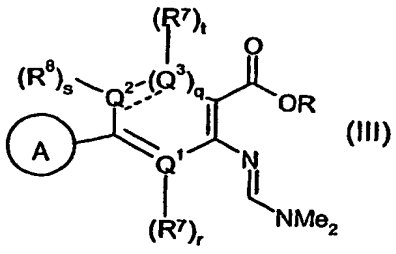
38. A process for preparing a compound of Claim 1 comprising reaction of a compound of formula (Va)



(Va)

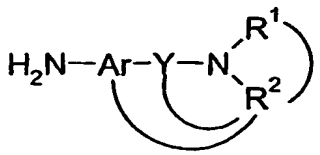
with a boronic acid and a palladium catalyst using a Suzuki coupling reaction or with an organostannane reagent and a palladium catalyst using a Stille coupling reaction and wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I) and T is a leaving group.

39. A process for preparing a compound of Claim 1 comprising coupling an amino ester of formula (III)



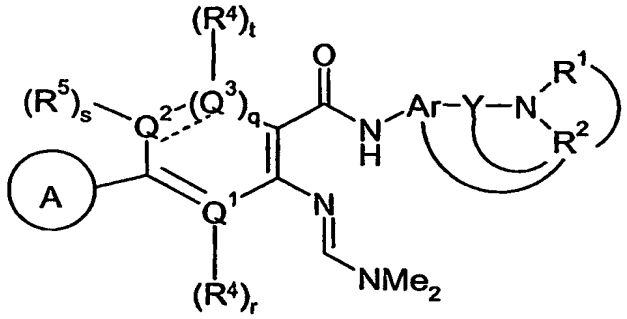
(III)

with an aniline of formula (II)



(II)

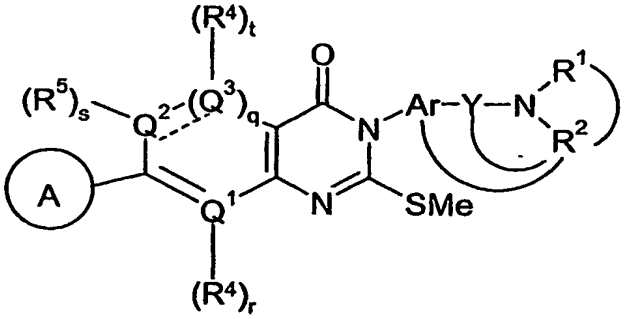
in a solvent in the presence of trimethylaluminum to produce a compound of formula (Vb)



(Vb)

and cyclizing said compound of formula (Vb) to form a compound of formula (I) and wherein wherein  , R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

40. A process for preparing a compound of Claim 1 wherein R^5 is hydrogen comprising reacting a sulfur-containing compound of formula (VI)



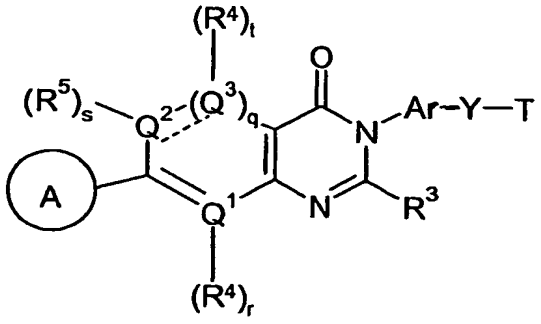
(VI)

with a Raney nickel reductant in the presence of a solvent and wherein wherein , R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

41. A process for preparing a compound of Claim 1 comprising the alkylation of an amine of formula (VII)

$H-NR^1R^2$ (VII)

with an alkylating agent of formula (VIII)



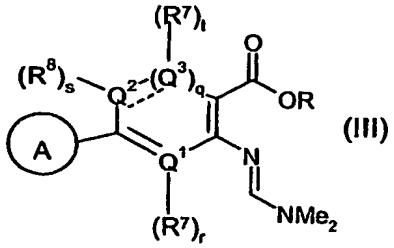
(VIII)

wherein T is a leaving group, and wherein A, R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

42. A process for preparing a compound of Claim 1 comprising the treatment of an amine of formula (VII)

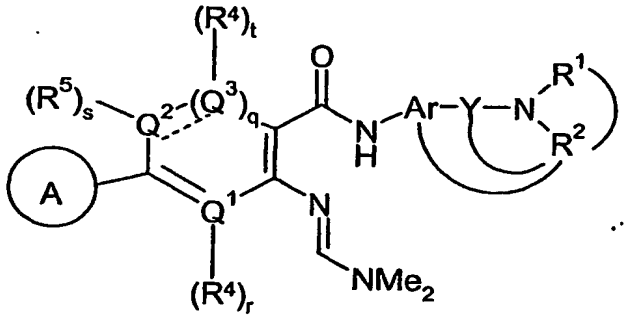
$H-NR^1R^2$ (VII)

with a strong base such as sodium hexamethyldisilazane and reaction with an ester of formula (III)

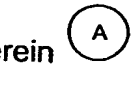


(III)

in a solvent such as tetrahydrofuran to produce a compound of formula (Vb)



(Vb)

and cyclizing said compound of formula (Vb) to form a compound of formula (I) and wherein wherein  , R^5, R^4, R^3, R^2, R^1, Ar, Y, Q^1, Q^2, Q^3, q, r, s, and t, are as defined in formula (I).

43. A method of treating obesity, diabetes, depression, or anxiety in a mammal comprising the administration to said mammal of an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

44. The method of Claim 43 wherein said mammal is a human.

45. A method of treating obesity, diabetes, depression, or anxiety in a mammal comprising the administration of an effective amount of a pharmaceutical composition containing a compound according to Claim 1, a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to said mammal.

46. The method of Claim 45 wherein said mammal is a human.

47. The compound of Claim 1, a salt, a solvate, or physiologically functional derivative thereof in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension, and an agent for treating arteriosclerosis.

48. The compound of Claim 1, a salt, a solveat, or a physiologically functional derivative thereof in combination with at least one species for the treatment of obesity selected from the group consisting of (i) human ciliary neurotrophic factor, (ii) a CB-1 antagonist or inverse agonist, (iii) a neurotransmitter reuptake inhibitor, (iv) a lipase inhibitor, (v) an MC4R agonist, (vi) a 5-HT2c agonist, and (vii) a ghrelin receptor agonist or antagonist.

49. A pharmaceutical composition comprising a compound of Claim 1 and at least one excipient or carrier.

50. The use of a compound of Claim 1 for the manufacture of a medicine for the treatment of a condition selected from the group consisting of obesity, diabetes, depression, and anxiety in a mammal preferably a human.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/010518

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 C07D519/00 A61K31/4985 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/82925 A (ISHIHARA YUJI ; SUZUKI NOBUHIRO (JP); TAKEKAWA SHIRO (JP); TAKEDA CHEM) 8 November 2001 (2001-11-08) cited in the application claim 1 & US 2004/077628 A1 (ISHIHARA YUJI ET AL) 22 April 2004 (2004-04-22)	1-50
P,X	WO 03/033476 A (WITTY DAVID RICHARD ; SMITHKLINE BEECHAM PLC (GB); HANDLON ANTHONY L () 24 April 2003 (2003-04-24) page 122, line 25 - line 31; claim 1	1-50

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2004	09/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seelmann, I

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0182925 A	08-11-2001	AU 5259601 A	12-11-2001
		CA 2407149 A1	08-11-2001
		EP 1285651 A1	26-02-2003
		WO 0182925 A1	08-11-2001
		JP 2002241274 A	28-08-2002
		US 2004077628 A1	22-04-2004
US 2004077628 A1	22-04-2004	AU 5259601 A	12-11-2001
		CA 2407149 A1	08-11-2001
		EP 1285651 A1	26-02-2003
		WO 0182925 A1	08-11-2001
		JP 2002241274 A	28-08-2002
WO 03033476 A	24-04-2003	CA 2463508 A1	24-04-2003
		CA 2463509 A1	24-04-2003
		CZ 20040498 A3	14-07-2004
		CZ 20040499 A3	18-08-2004
		EP 1442025 A1	04-08-2004
		EP 1436267 A1	14-07-2004
		WO 03033476 A1	24-04-2003
		WO 03033480 A1	24-04-2003